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THE UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES ON SOME LYCOPODIUM ALKALOIDS

BY

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B.Sc. (HON.)

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Synthetic Studies on Some Lycopodium Alkaloids." submitted by Kenneth Piers B.Sc.(Hon.) in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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A B S T R A C T

The transformation of lycopodine into annofoline via an unsaturated amido acetate has been carried out. This transformation is of biogenetic interest since lycopodine has been postulated to be the central intermediate in the biosynthesis of the *Lycopodium* alkaloids.

The transformation of the unsaturated amido acetate obtained above into lycopodine has been carried out. This transformation is of potential use in the total synthesis of lycopodine since it provides a synthetic method of controlling the stereochemistry of the C-15 methyl group.

The total synthesis of the cernuine ring skeleton has been achieved thus confirming the structural assignment made for the alkaloids cernuine and lycocernuine. The total synthesis was also useful in confirming the stereochemistry of the naturally occurring compounds.

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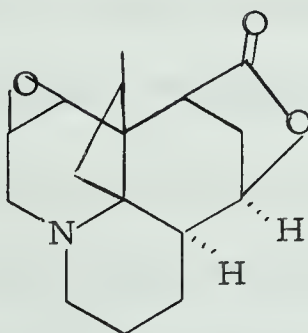
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INTRODUCTION

In recent years a considerable number of publications dealing with the structures of a variety of Lycopodium alkaloids have appeared. These publications have stimulated interest in synthetic approaches to these alkaloids both from the viewpoint of interconversions within the group and also toward the total synthesis of the alkaloids.

Another reason for attempting the total or partial synthesis of a naturally occurring compound is of course provided by the intellectual challenge in devising and carrying out such a synthesis. Furthermore, in a synthetic problem, considerable effort is devoted to the development of new synthetic methods and also to the refinement of synthetic methods now in use.

The structure of the alkaloid annotinine (II) was first published in 1957 (3), a proposal which was confirmed by X-ray

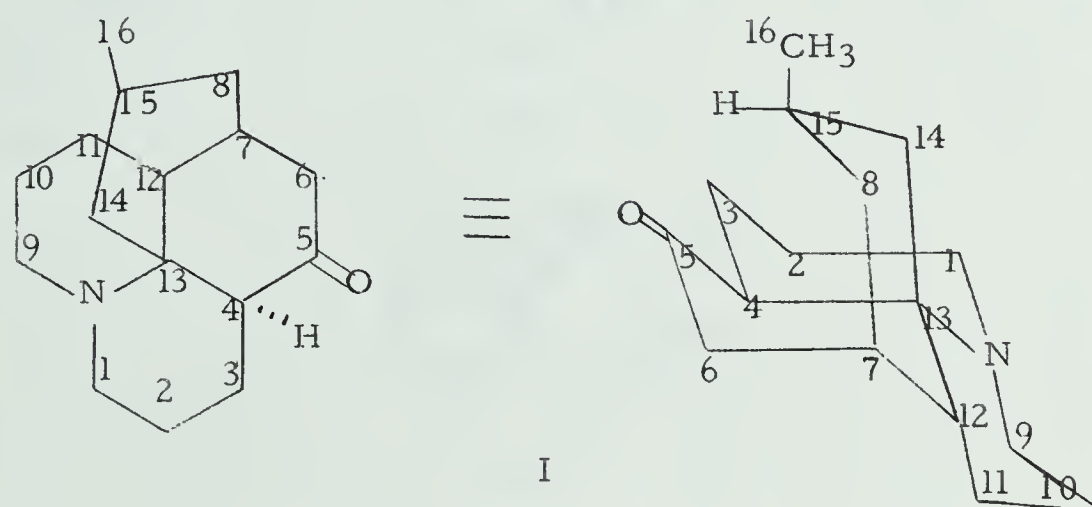


II

crystallographic studies (4, 5). The later publication (5) also indicated

the relative stereochemistry of the alkaloid. Annotinine (II) is unique among the Lycopodium alkaloids in that it is the only one to date which has been found to incorporate a cyclobutane ring into its skeleton.

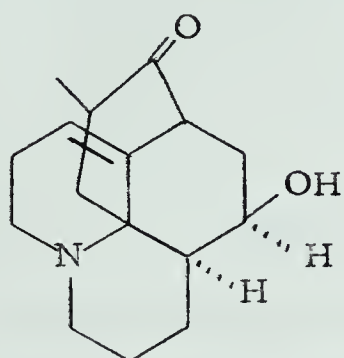
After intensive investigation by several groups, MacLean and co-workers (1) proposed the structure (I) for lycopodine, the major alkaloid present in several species of the Lycopodium Family. Most



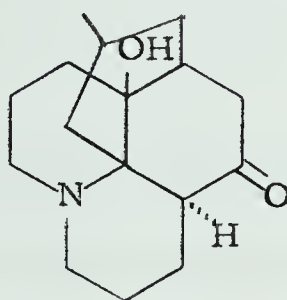
of the Lycopodium alkaloids known to date are characterized by containing the lycopodine-type ring skeleton. The relative configuration of lycopodine as shown in structure (I) was originally proposed by Anet (2) in 1960 and the absolute stereochemistry of both lycopodine (I) and annotinine (II) was determined by Wiesner (6) in 1961. In the case of lycopodine (I) the absolute stereochemistry has been confirmed by an application of the axial halo-ketone rule (7).

After the structural determination of lycopodine (I) had been completed, the structures of several other Lycopodium alkaloids were quickly elucidated. Many of these, among which are acrifoline (III) (8), lycodoline (IV) (9) and annofoline (V) (10), have the same

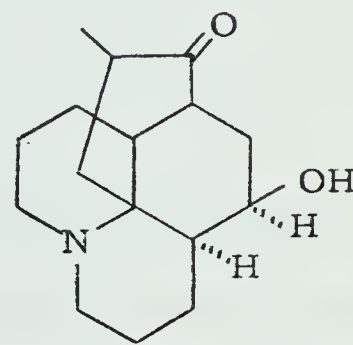
structural skeleton as lycopodine. Recently the alkaloid lyconnotine has been shown to have structure VI (11), a structure which represents a departure from the usual lycopodine-type skeleton.



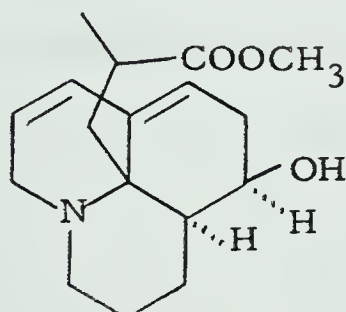
III



IV

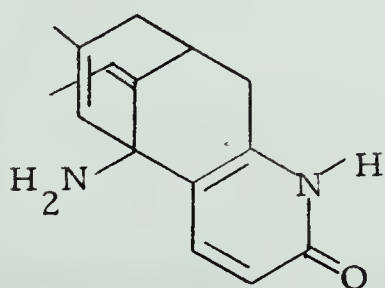


V

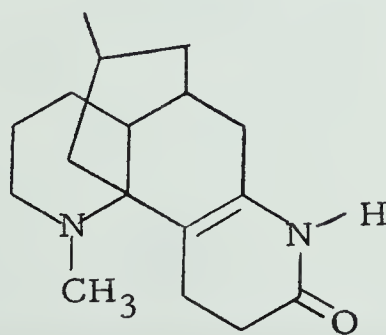


VI

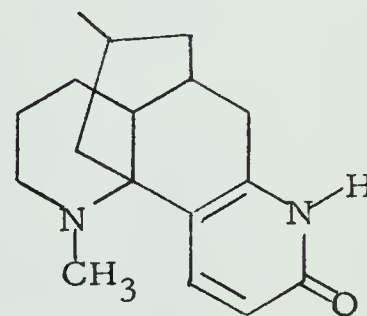
A second group of *Lycopodium* alkaloids which are dinitrogenous and which have a skeleton somewhat different from that of lycopodine was first reported in 1960. Representative alkaloids of this group include selagine (VII) (11), α -obscurine (VIII) and β -obscurine (IX) (12) and lycodine (X) (13).



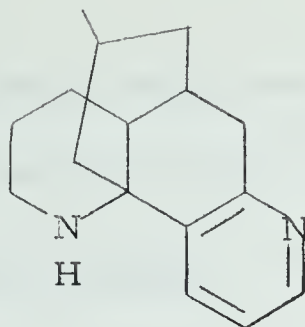
VII



VIII

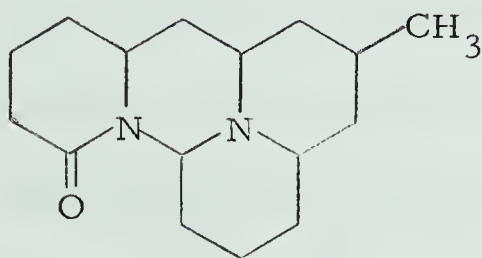


IX

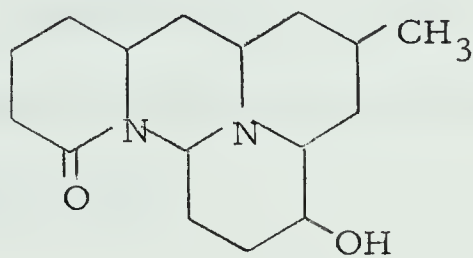


X

More recently Ayer, Jenkins and Valverde-Lopez (15) have proposed structures for two new alkaloids cernuine (XI) and lycocernuine (XII), the major alkaloids from the plant Lycopodium cernuum. These two alkaloids represent a third structural type of Lycopodium alkaloid



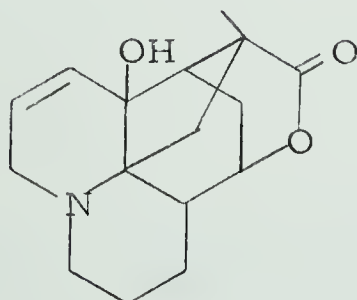
XI



XII

and represent a major departure from the more usual type of skeleton as present in lycopodine (I).

MacLean and co-workers (33 a, b) have recently published the structure of the alkaloid annotine (XIII), an alkaloid which is of some

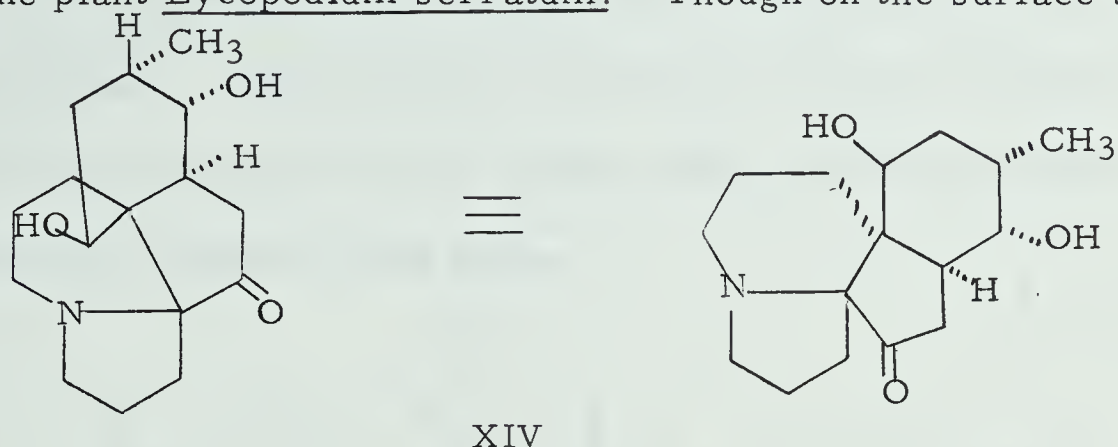


XIII

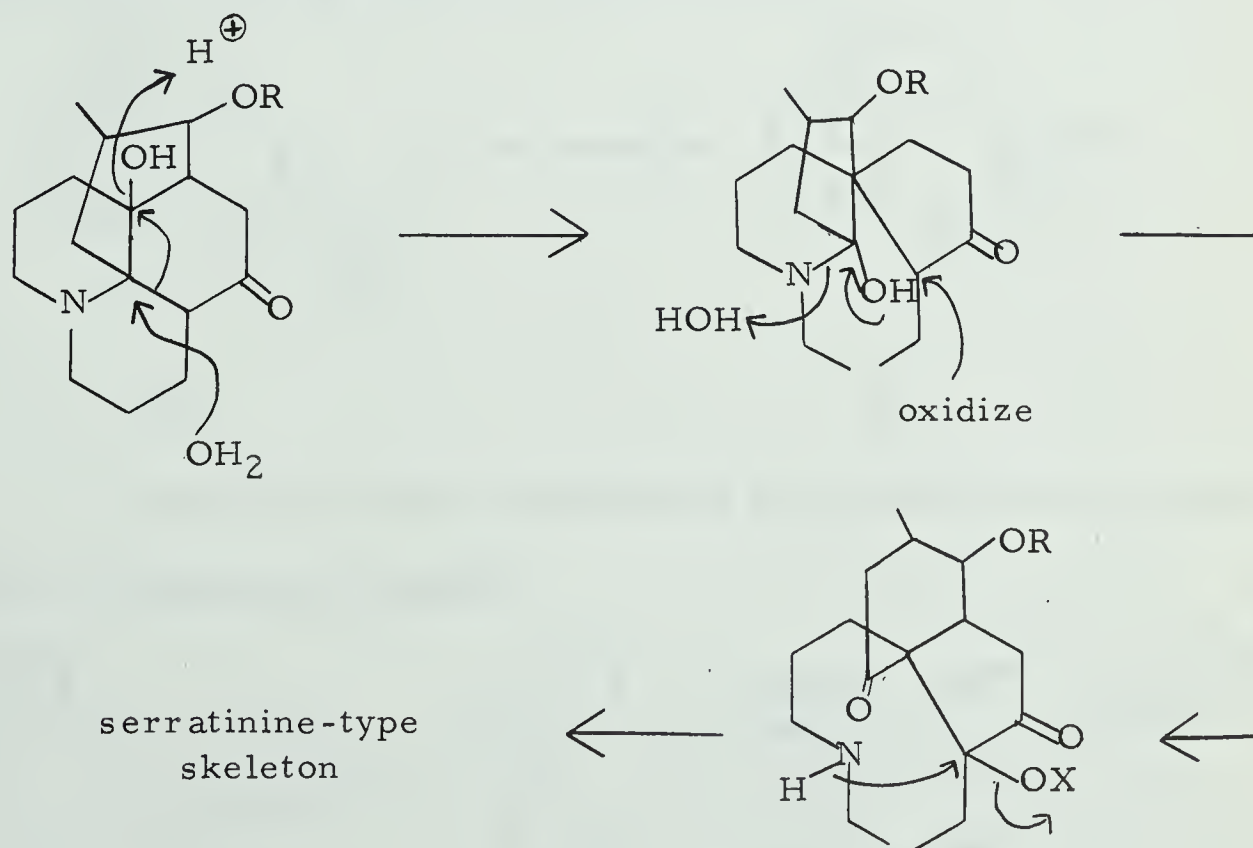
interest since it contains a five membered bridging ring.

Very recently a fourth structural type of Lycopodium alkaloid

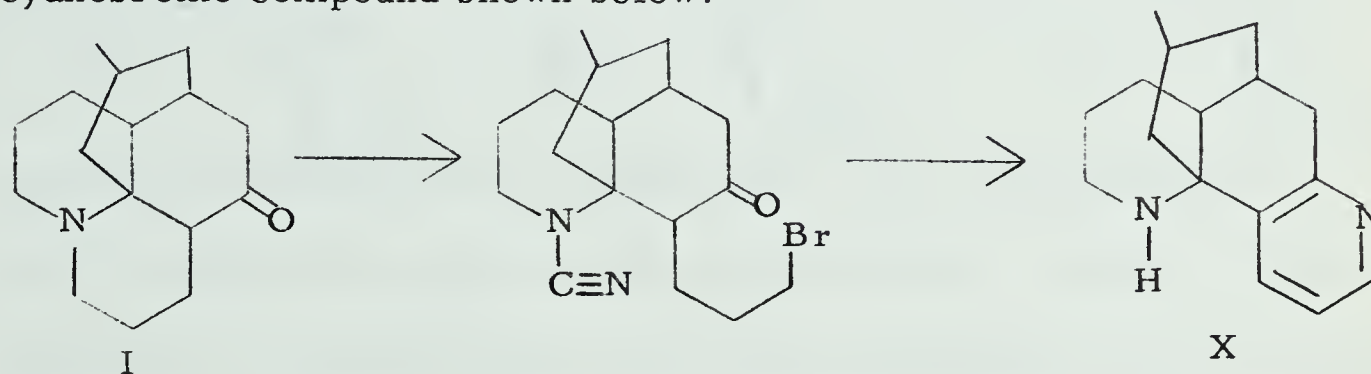
has been recognized. Inubushi and co-workers have published the structure (18) and stereochemistry (19) of serratinine (XIV) an alkaloid from the plant Lycopodium serratum. Though on the surface the



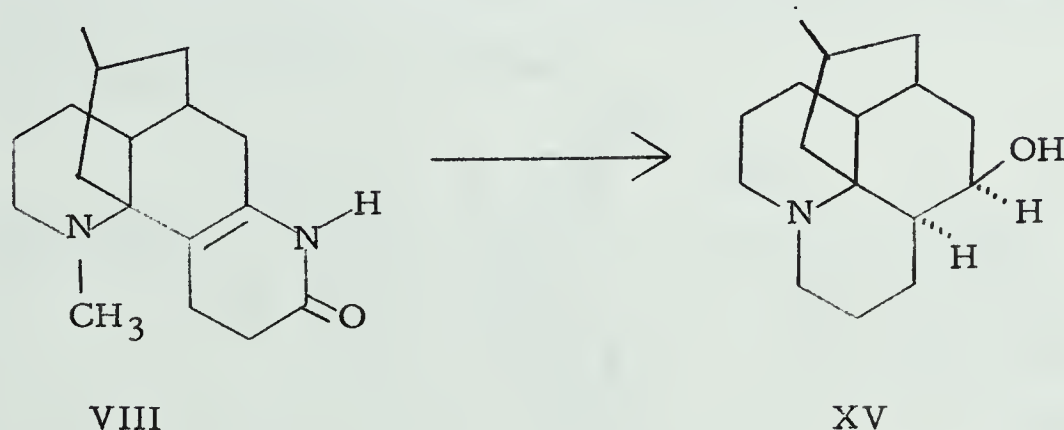
structure of serratinine (XIV) appears to differ markedly from that of the more usual Lycopodium alkaloids, hypothetically at least, it can be readily arrived at by suitable rearrangement and oxidation of the usual lycopodine-type skeleton as shown below.



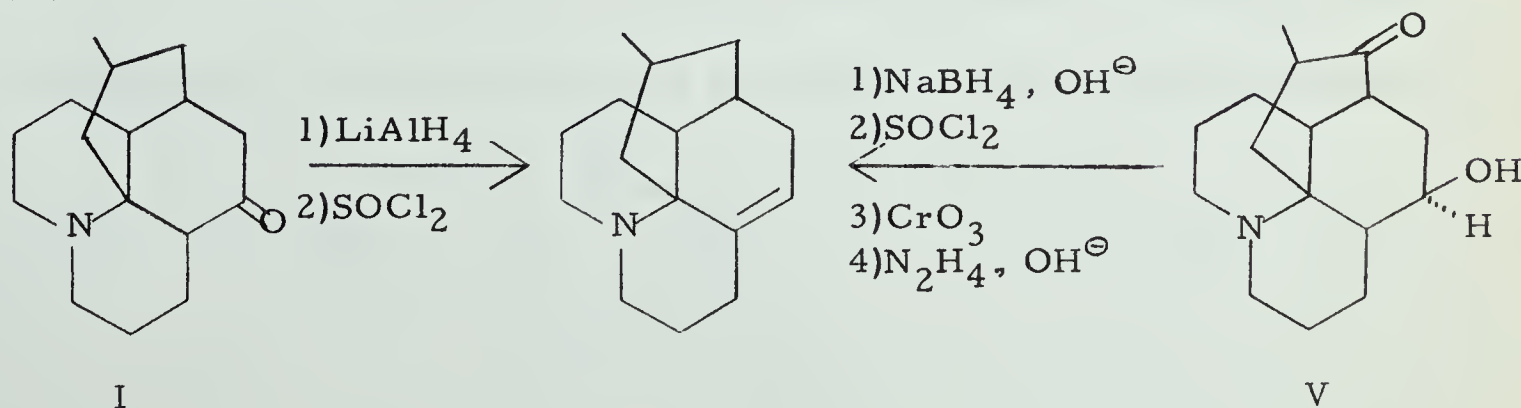
There have been only a limited number of publications dealing with the synthetic aspects of Lycopodium chemistry to date and several of these have been concerned only with transformations within various groups. Thus Anet and Rao (16) have carried out the transformation of lycopodine (I) into lycodine (X) via the intermediate cyanobromo compound shown below.



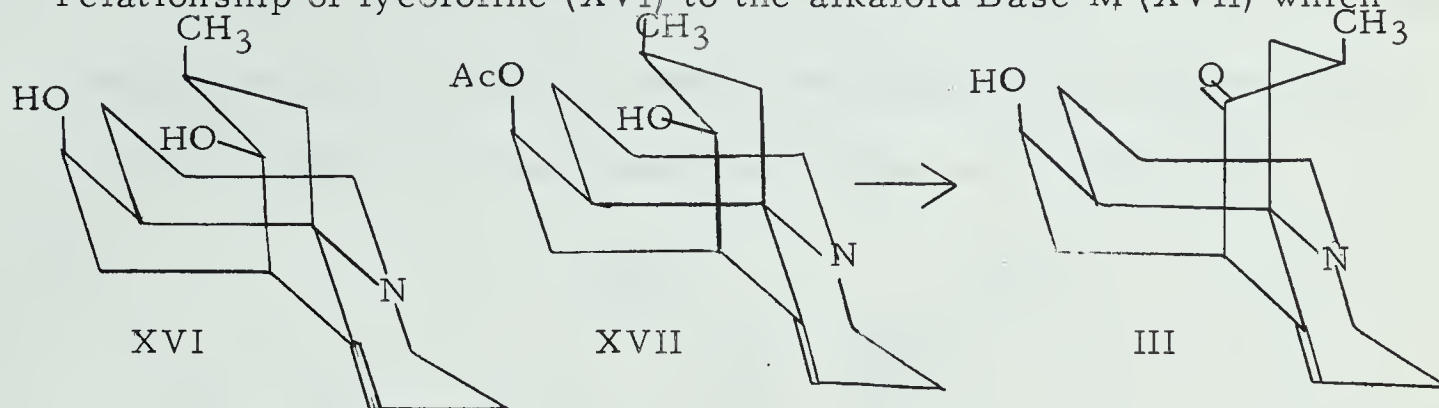
Ayer and co-workers (13) have reported the conversion of α -obscurine (VIII) into dihydrolycopodine (XV).



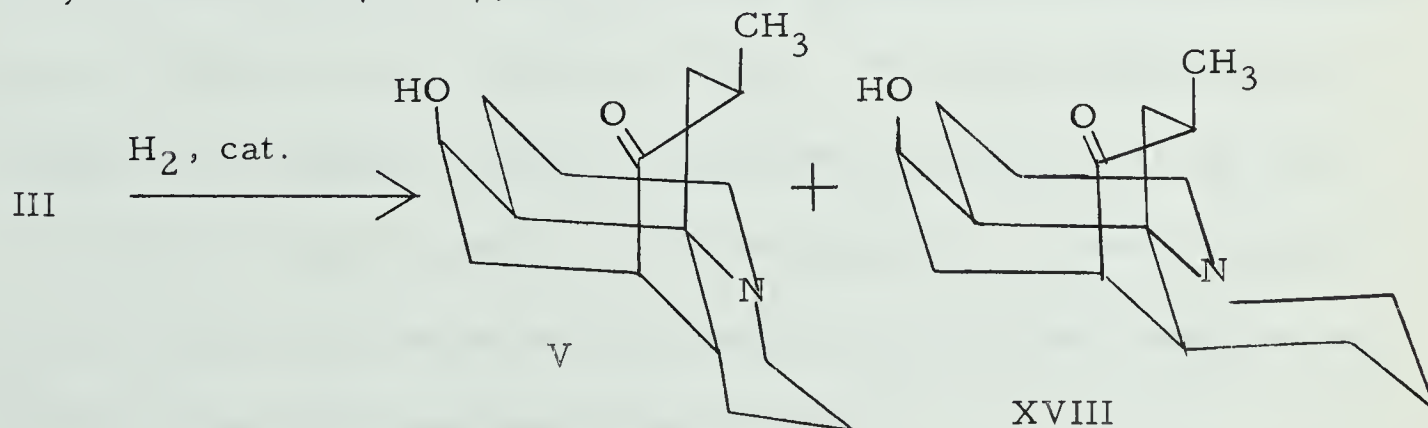
Anet (17) has also transformed lycopodine (I) and annofoline (V) into a common intermediate.



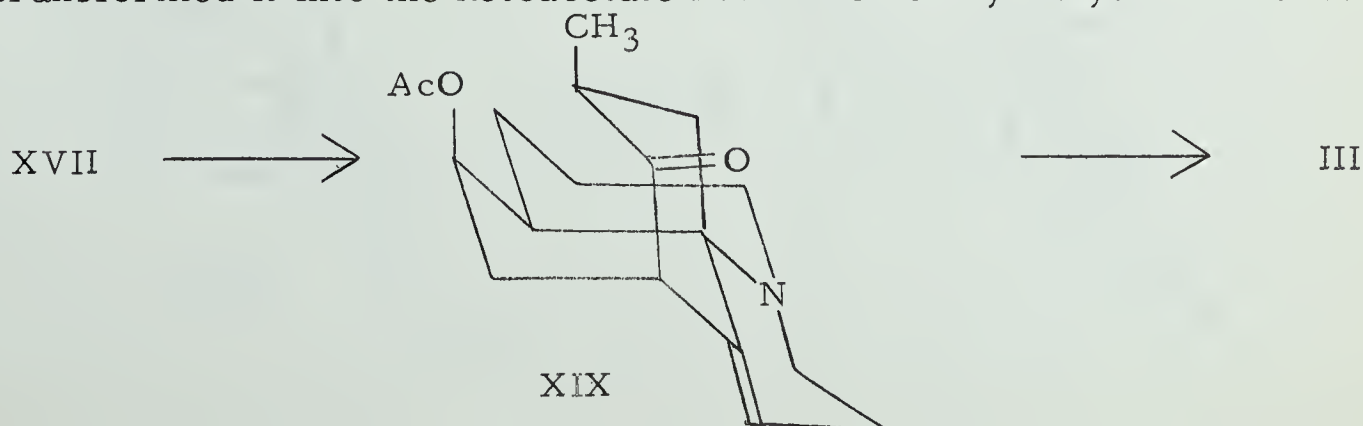
In 1962 Burnell and Taylor (34) reported the correlation of the alkaloid lycofoline (XVI) with acrifoline (III) by first showing the relationship of lycofoline (XVI) to the alkaloid Base M (XVII) which



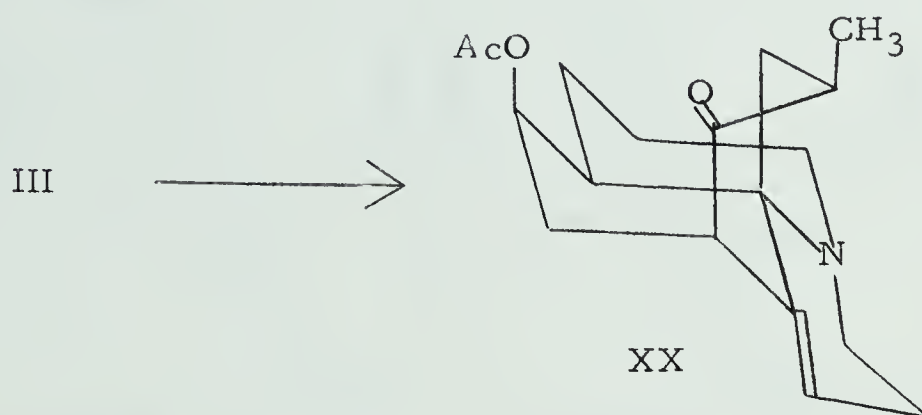
was then transformed into acrifoline (III). The transformation of Base M (XVII) into acrifoline (III) requires further comment. The structure of acrifoline (III) was determined by MacLean and co-workers (35) and its stereochemistry follows from the fact that on catalytic hydrogenation (17) a small amount of annofoline (V), in addition to dihydroacrifoline (XVIII), is formed.



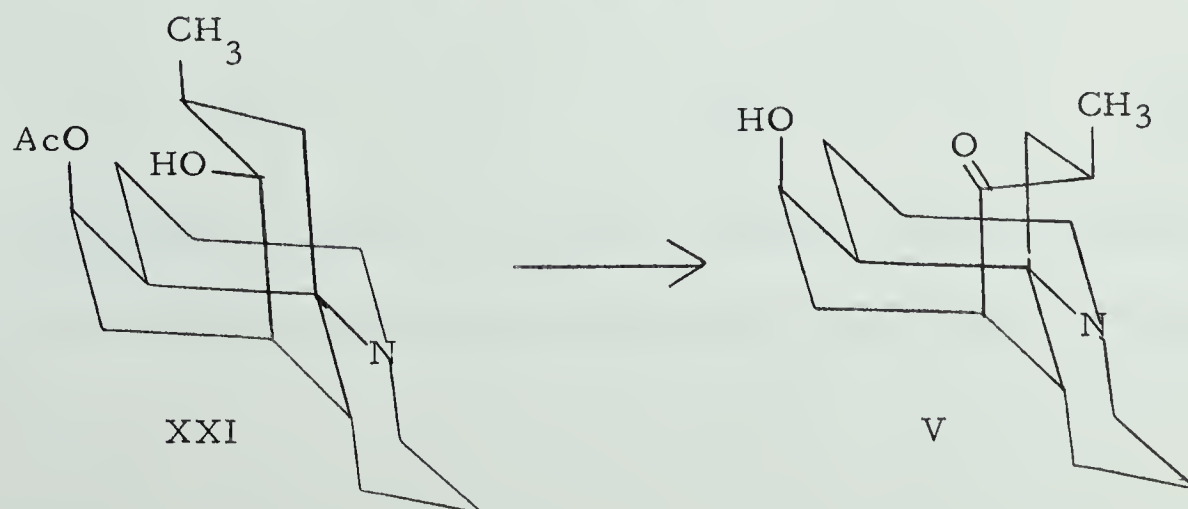
Oxidation of Base M (XVII) with chromium trioxide-pyridine transformed it into the ketoacetate XIX which on hydrolysis in methanolic



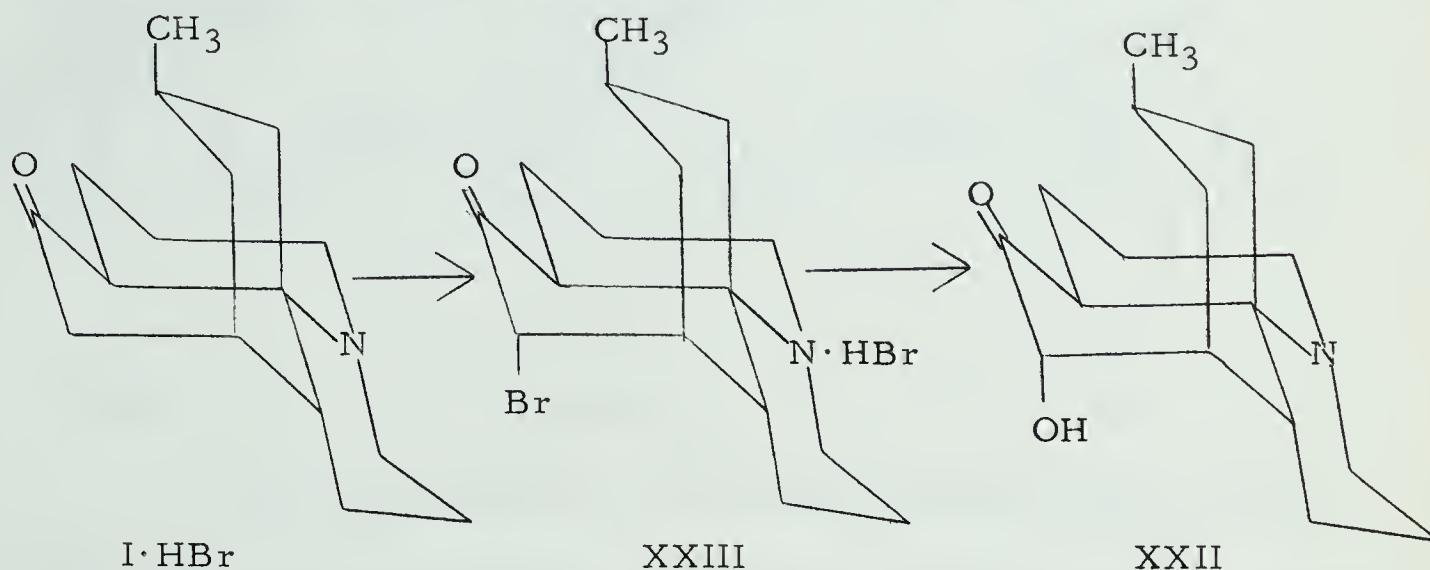
hydroxide yielded acrifoline (III). However acetylation of acrifoline under non-basic conditions gave a keto acetate which was not identical to the keto acetate XIX obtained from Base M (XVII). The keto acetate obtained from acrifoline (III) must then differ in stereochemistry at the C-15 methyl group and hence must have the structure XX.



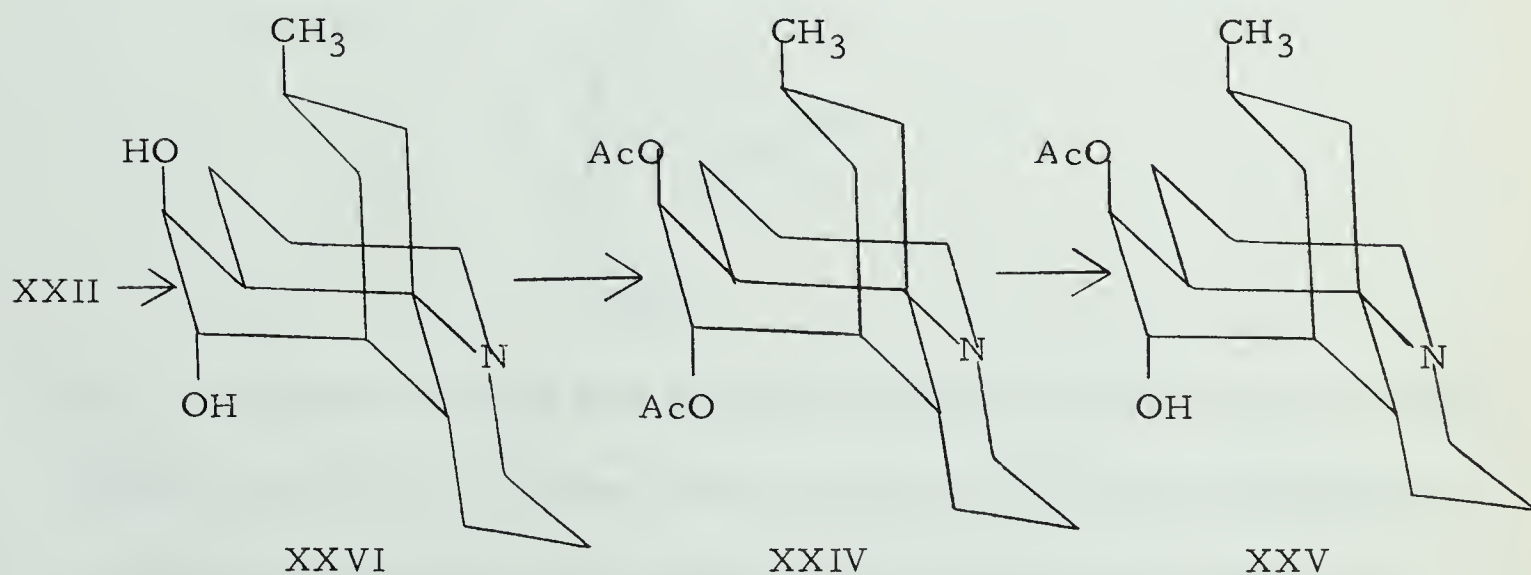
Hence the transformation of the keto acetate XIX into acrifoline (III) must take place by hydrolysis of the acetoxy function with simultaneous epimerization of the C-15 carbon atom, which then causes the bridging ring to flip to the more stable boat form. The boat conformation is favored here because it relieves steric interaction between the axial C-5 hydroxyl function and the C-15 methyl group. A similar type of epimerization and conformational change occurs in the transformation of fawcettiine (XXI) into annofoline (V) (36).



The conversion of lycopodine (I) into alkaloid L-20 (XXII) was reported (7) in 1963. Bromination of lycopodine hydrobromide ($I \cdot HBr$) yielded 6 α -bromolycopodine hydrobromide (XXIII) which on treatment with 5% aqueous sodium bicarbonate gave alkaloid L-20 (XXII).



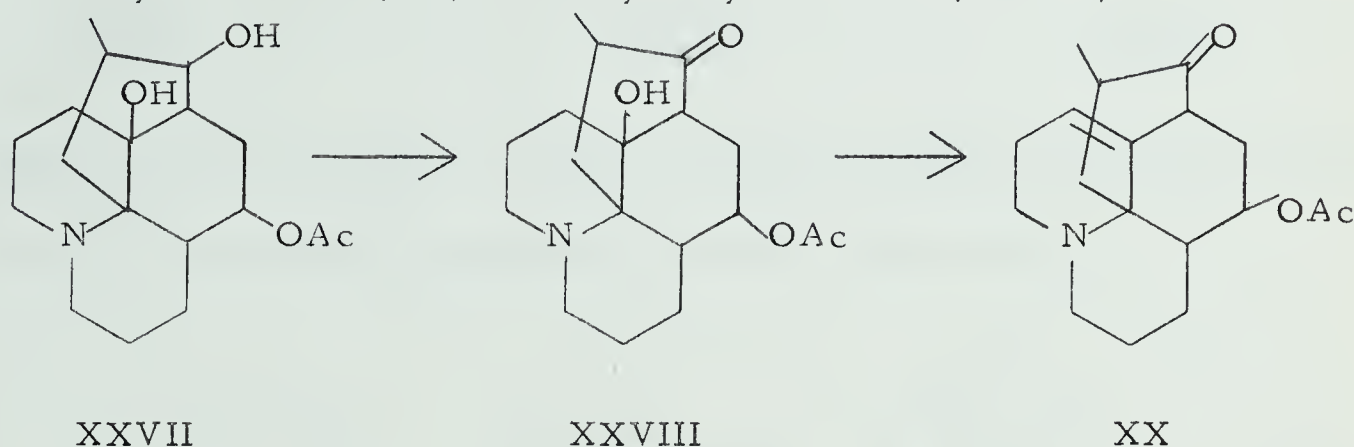
Ayer and Law (37) have reported the conversion of alkaloid L-20 (XXII) into acetyllycoclavine (XXIV) which in turn has been



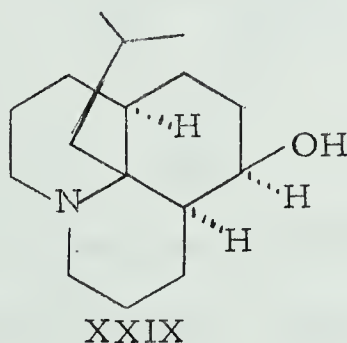
hydrolyzed to lyococlavine (XXV). Lithium aluminum hydride reduction of L-20 (XXII) gave desacetyllycoclavine (XXVI) which on acetylation in

acetic anhydride-pyridine yielded acetyllycoclavine (XXIV).

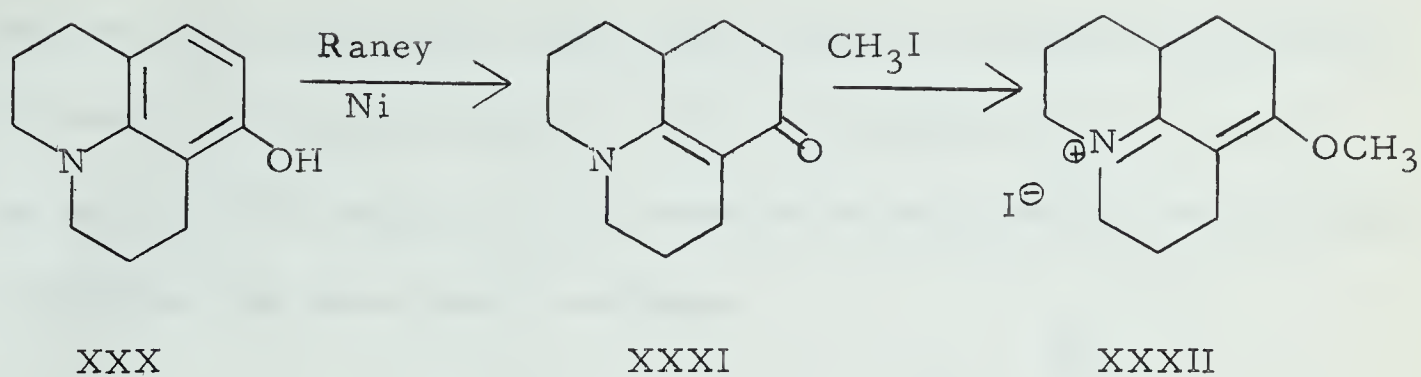
More recently Ayer and co-workers (38) have reported the structure of lycofawcine (XXVII) which they have transformed into O-acetylacrifoline (XX) via dehydrolycofawcine (XXVIII).



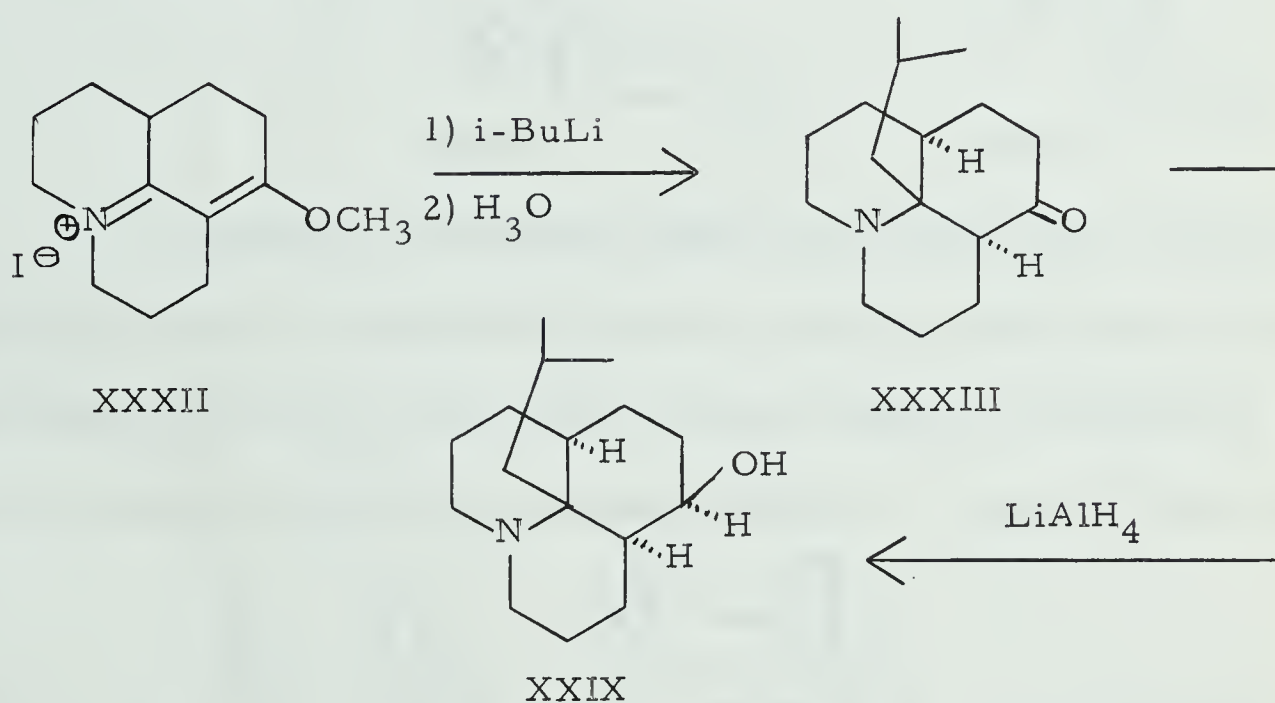
By total synthesis of the racemic alcohol XXIX, Wiesner, Valenta and co-workers (20) have confirmed the structure of lyconnotine (VI). The alcohol XXIX is a transformation product of lyconnotine (VI). Their synthesis, which represents the first entry into the lycopodine



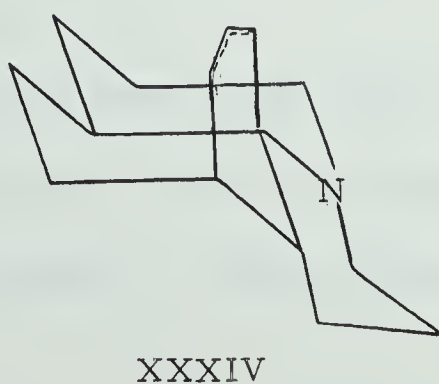
type ring system starting with readily available starting materials, began with the phenol XXX. Raney nickel reduction of the phenol XXX gave the α,β -unsaturated ketone XXXI which was converted to the immonium iodide XXXII by refluxing with methyl iodide. Alkylation of the salt XXXII with isobutyl lithium followed by acid hydrolysis of the enol ether function



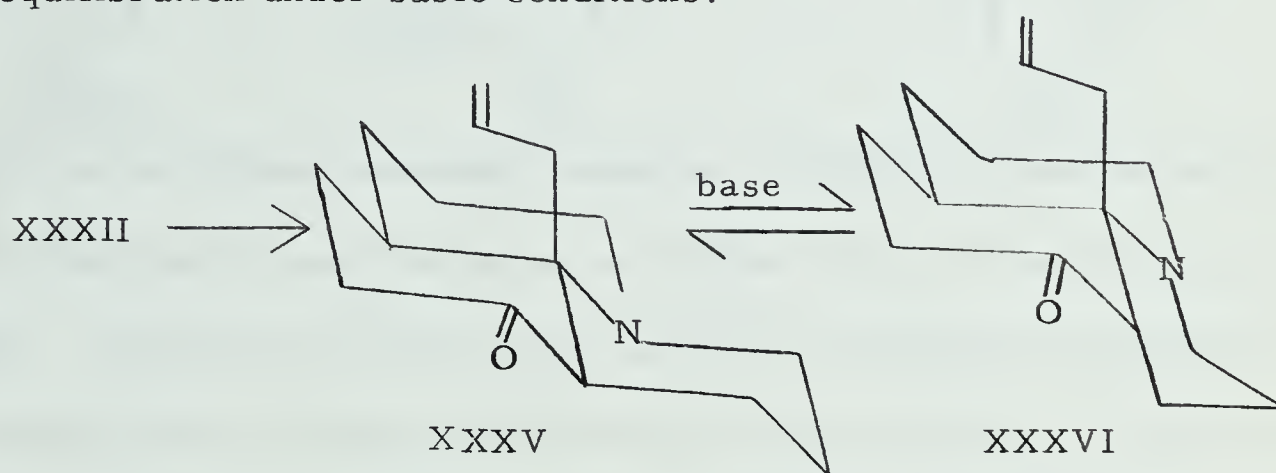
gave the ketone XXXIII. Finally, lithium aluminum hydride reduction of the ketone XXXIII yielded the racemic alcohol XXIX.



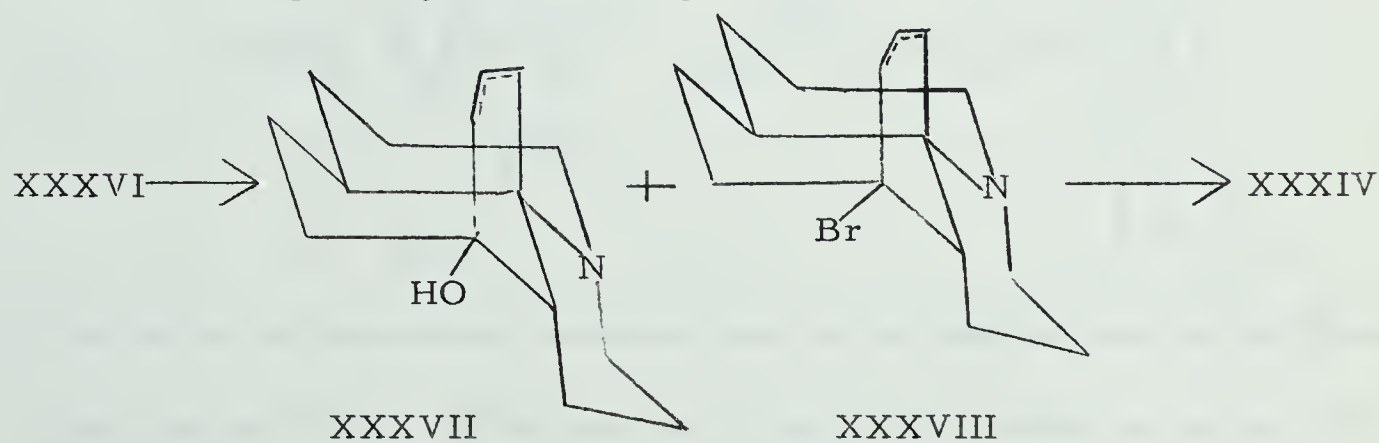
In attempts to develop methods for the total synthesis of the Lycopodium alkaloids Wiesner, Valenta and co-workers (21) have reported the synthesis of the tetracyclic compound XXXIV which contains all but one of the asymmetric carbon atoms of the alkaloid lycopodine (I).



Reaction of the immonium iodide XXXII with allyl magnesium bromide followed by mild acid hydrolysis of the intermediate enol ether gave the ketone XXXV which could be converted to the isomeric ketone XXXVI by equilibration under basic conditions.



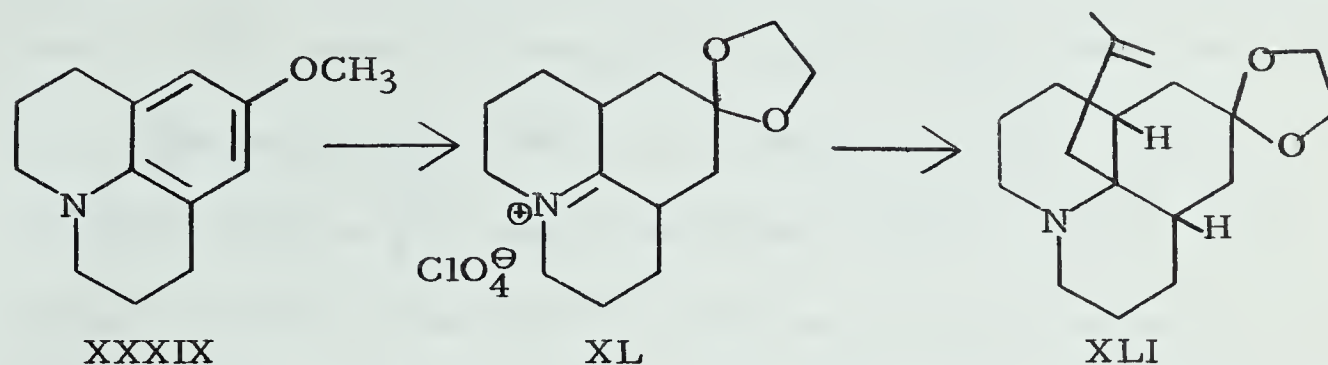
Treatment of the ketone XXXVI with 70% sulfuric acid gave a high yield of the alcohol XXXVII whereas reaction of the ketone XXXVI with boiling hydrobromic acid gave a mixture of the alcohol XXXVII and the corresponding bromo-compound XXXVIII. Chemical reduction



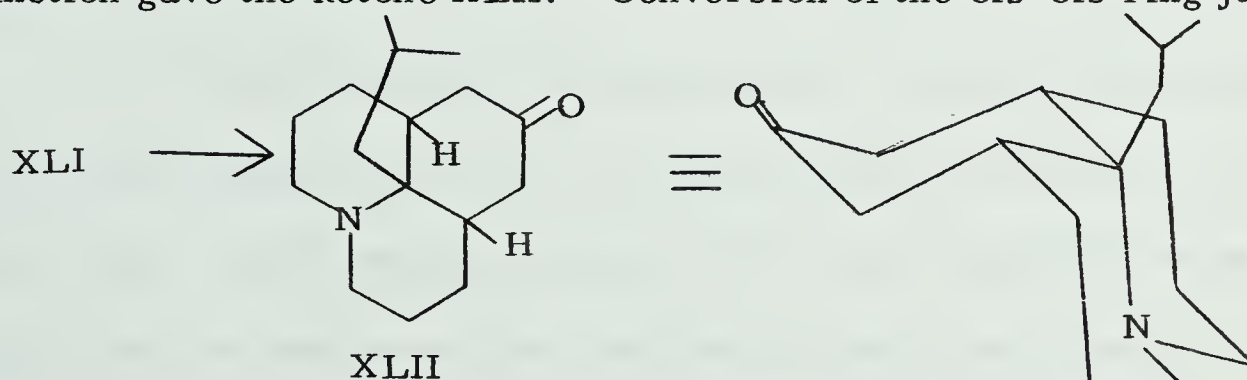
of the bromo-compound XXXVIII with sodium amalgam yielded the tetracyclic amine XXXIV.

In a very recent publication Ayer and co-workers (22) describe a different approach to the total synthesis of the Lycopodium alkaloids similar to lycopodine. Beginning with the readily available

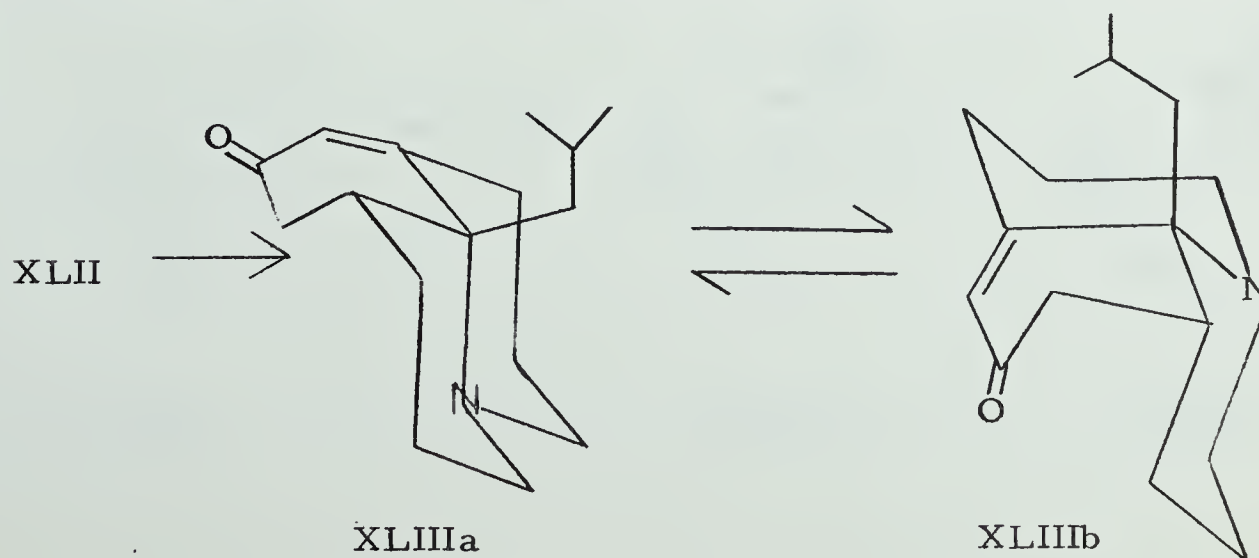
9-methoxyjulolidine (XXXIX), the ketal immonium perchlorate XL was



prepared by lithium-ammonia reduction of XXXIX followed by ketalization and simultaneous salt formation in ethylene glycol containing perchloric acid. Reaction of the immonium salt XL with methallyl magnesium bromide gave the unsaturated ketal XLI which was shown to have the cis-cis stereochemistry at the ring junctions. Catalytic hydrogenation of the unsaturated ketal XLI followed by acid hydrolysis of the ketal function gave the ketone XLII. Conversion of the cis-cis ring junction

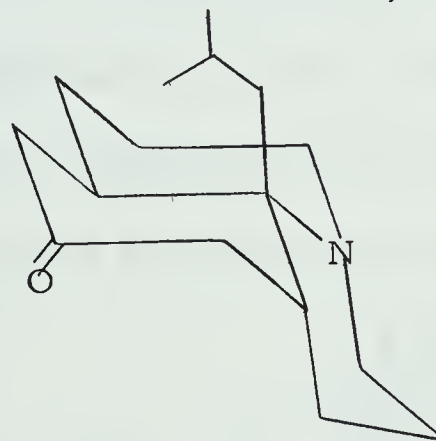


to the required cis-trans compound was accomplished via the α,β -unsaturated ketone XLIII. Bromination of the hydrobromide of ketone XLII



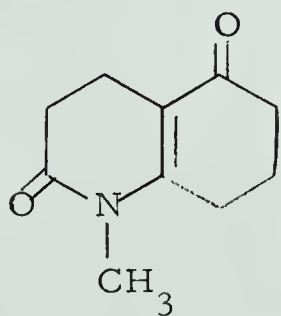
followed by dehydrobromination via the semicarbazone gave, after removal of the semicarbazone function, the α,β -unsaturated ketone which appeared to exist mainly in conformation XLIIIb. Chemical reduction of the α,β -unsaturated ketone XLIII gave a new ketone isomeric with the ketone XLII to which was assigned the structure XLIV which is now in the same configuration as the normal Lycopodium alkaloids.

XLIII

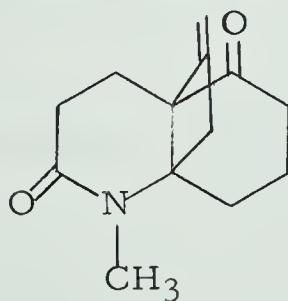


XLIV

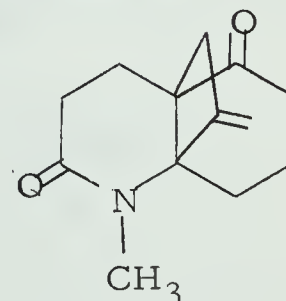
In a continuation of their efforts in the total synthesis of Lycopodium alkaloids Wiesner, Valenta and Bohner (23) have recently described a photochemical approach to the annotinine (II) skeleton. Thus when the unsaturated keto lactam XLV was photolyzed in the presence of excess allene two olefins XLVI and XLVII were obtained. Catalytic



XLV

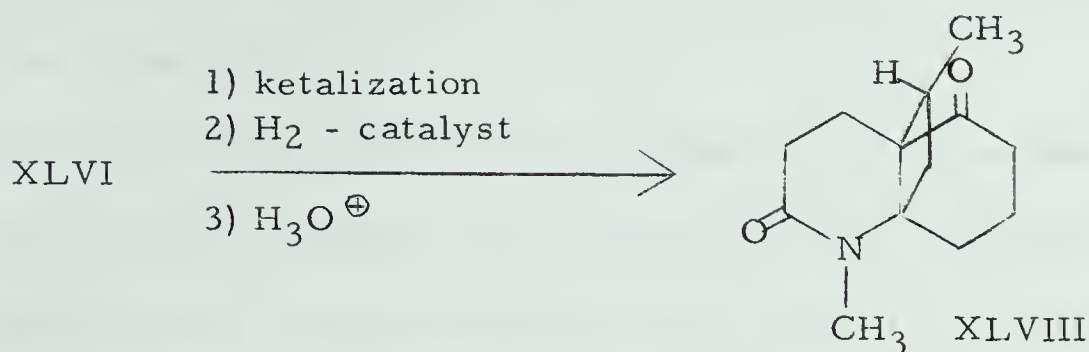


XLVI

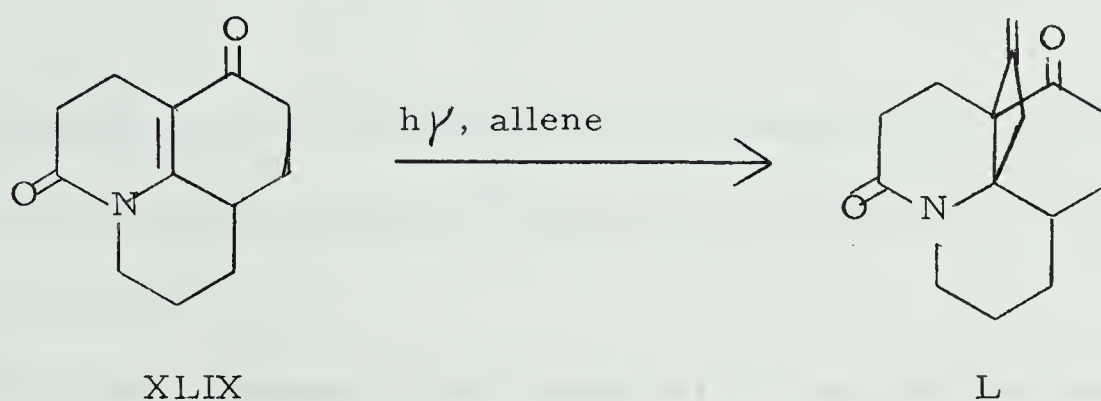


XLVII

hydrogenation of the ethylene ketal of the olefin XLVI followed by removal of the ketal function gave only the ketone XLVIII.

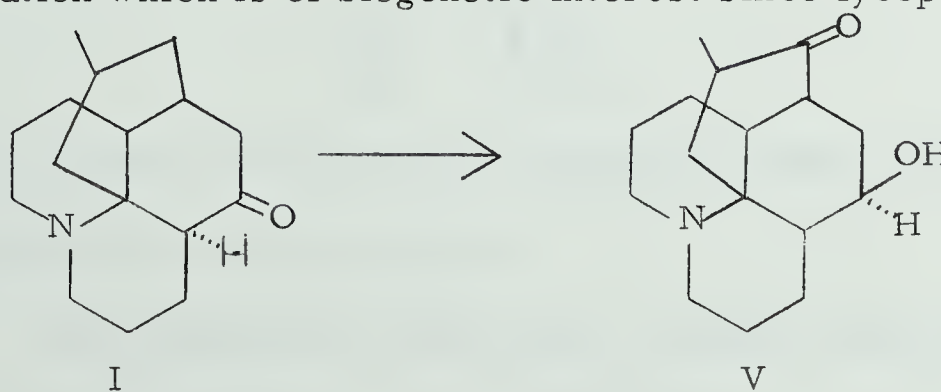


These workers hope to gain an entry to the annotinine skeleton by photochemical reaction of a substrate such as XLIX with allene to yield a product with a structure similar to that shown in L.



The present work consisted of three different synthetic problems which are outlined briefly below.

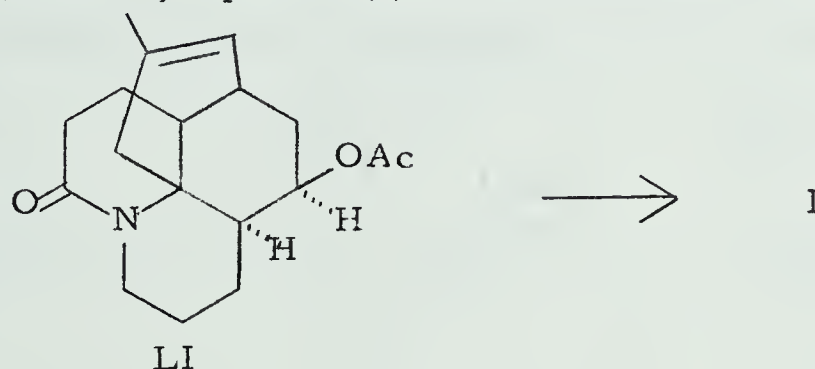
1) The transformation of lycopodine (I) into annofoline (V) is a transformation which is of biogenetic interest since lycopodine (I) has



been postulated (24) to be the central intermediate in the biogenesis of

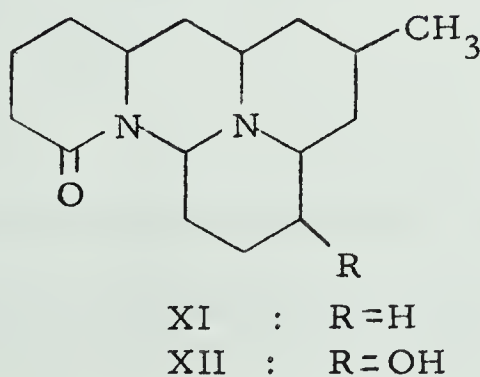
Lycopodium alkaloids. It has been proposed that lycopodine (I) may be transformed into alkaloids of the annofoline (V) and the annotinine (II) type in the plant.

2) The transformation of the unsaturated amido acetate LI, a key intermediate obtained in the transformation of lycopodine (I) into annofoline (V), into lycopodine (I) was carried out since this sequence is



of potential use in the total synthesis of lycopodine (I) as it provides a synthetic method of controlling the stereochemistry of the C-15 methyl group.

3) The total synthesis of the cernuine (XI) ring skeleton was undertaken



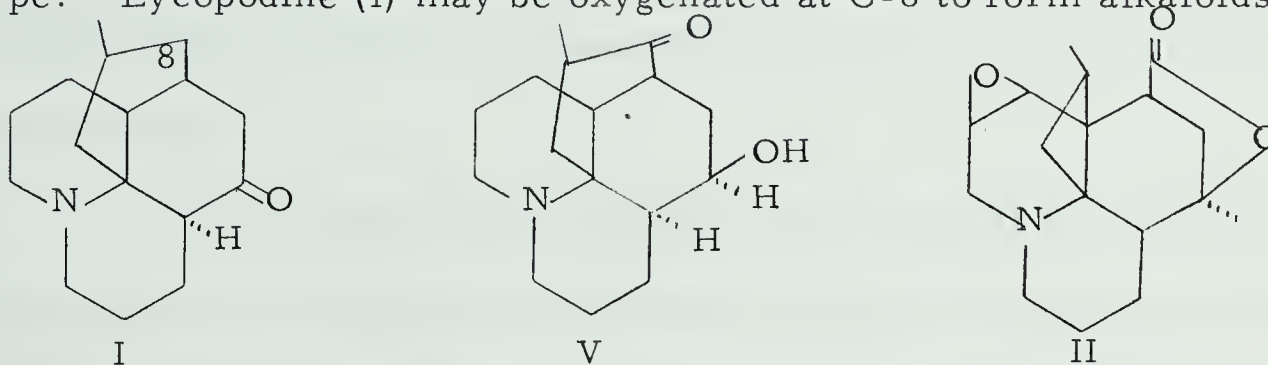
in order to confirm the structural assignment made (15) for the alkaloids cernuine (XI) and lycocernuine (XII).

These problems will be dealt with under separate headings in the section entitled "Discussion and Results".

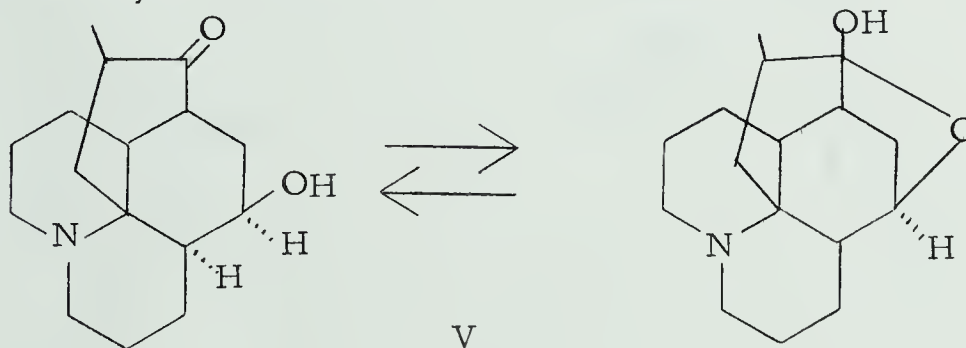
DISCUSSION AND RESULTS

A. THE TRANSFORMATION OF LYCOPODINE (I) INTO ANNOFOLINE (V)

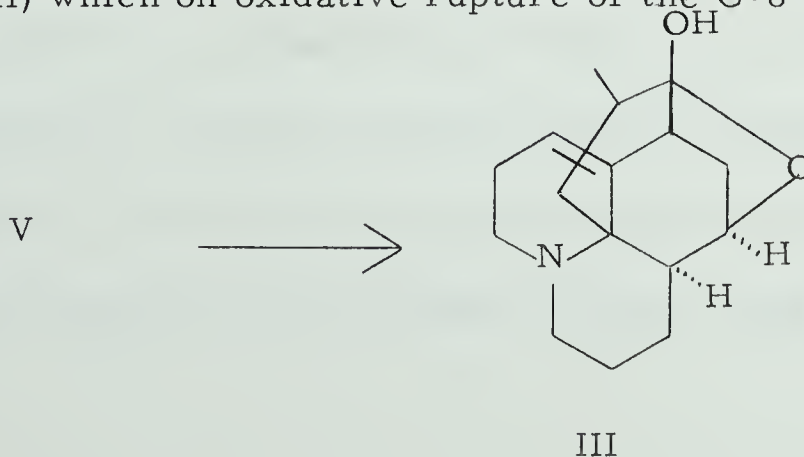
It has been suggested (24) that lycopodine (I) may be the biogenetic precursor of alkaloids of the annofoline (V) and annotinine (II) type. Lycopodine (I) may be oxygenated at C-8 to form alkaloids of the



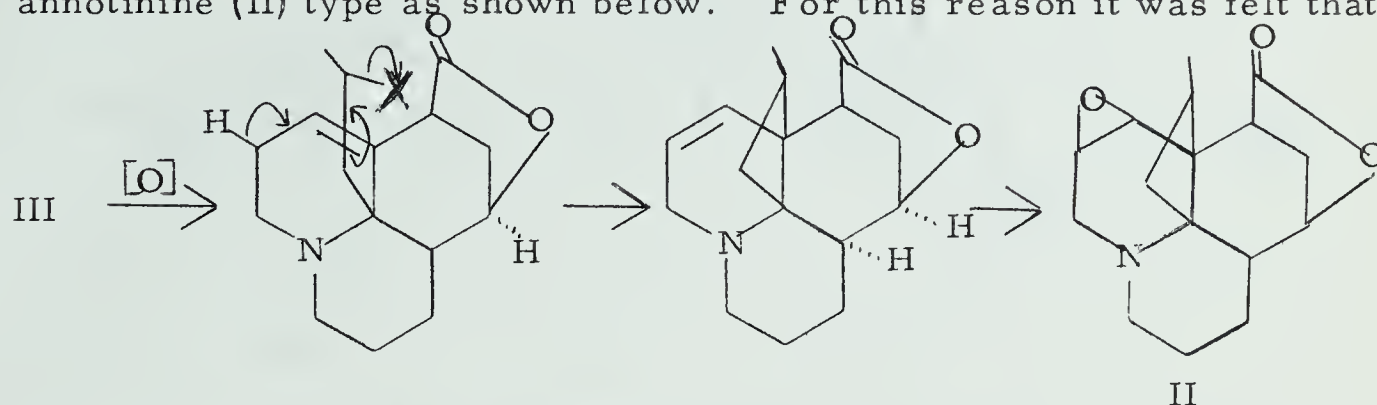
annofoline (V) type. The close similarity of annofoline (V) to annotinine (II) is more readily seen from the hemiketal form of annofoline (V).



Enzymatic dehydrogenation of annofoline (V) could lead to acrifoline (III) which on oxidative rupture of the C-8 to C-15 bond, followed

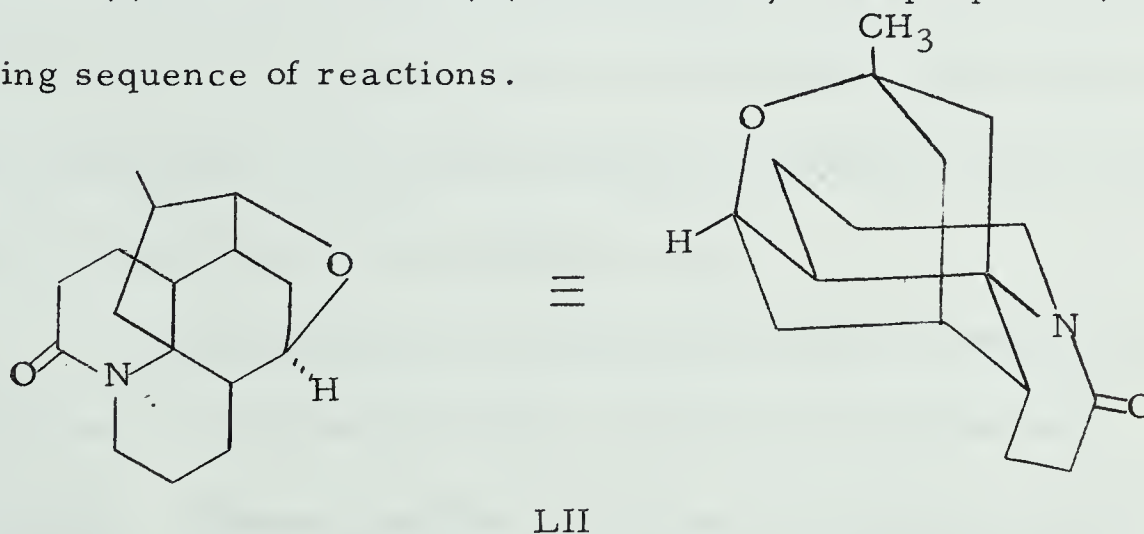


by ring closure and then epoxidation could lead to alkaloids of the annotinine (II) type as shown below. For this reason it was felt that

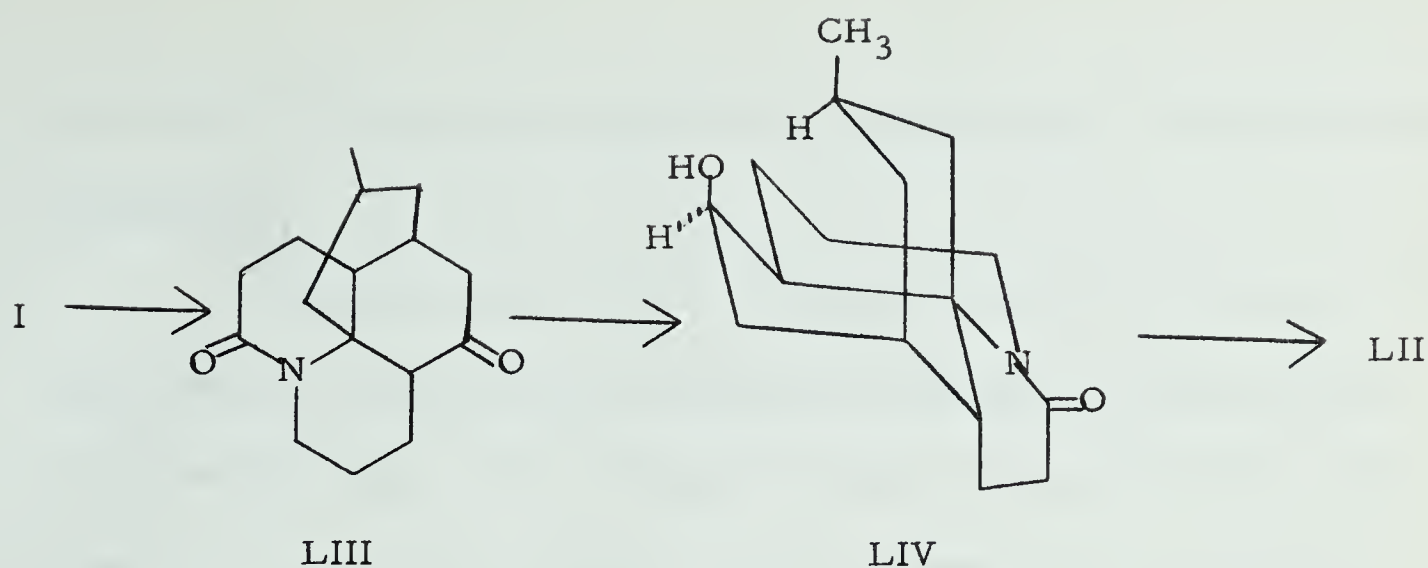


the laboratory conversion of lycopodine (I) into annofoline (V) would be of interest.

At the time that the present work was begun, the 5,15-amido ether LII, one of the key intermediates to be used in the conversion of lycopodine (I) into annofoline (V), had already been prepared (25) by the following sequence of reactions.



Oxidation of lycopodine (I) with neutral potassium permanganate in acetone yielded the corresponding lactam LIII in 20-30% yield. This step was necessary in order to protect the basic nitrogen in later steps in the synthesis. The lactam so obtained was identical with the so-called lactam previously prepared by MacLean (28) using a less direct method.



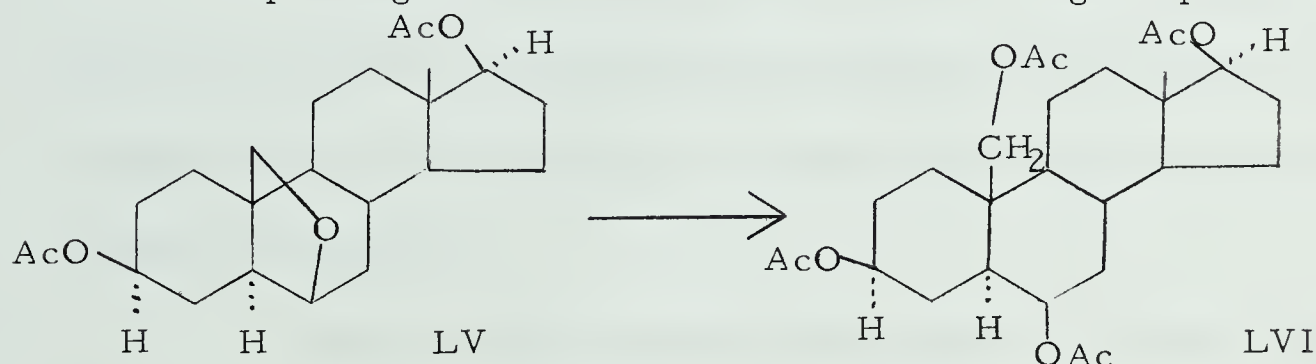
Sodium borohydride reduction of the lactam LIII gave, in nearly quantitative yield, the β -hydroxy lactam LIV (substituents on the same side as the bridging ring carrying the methyl group designated β , those on the opposite side are α).

Lead tetraacetate oxidation (26) of the hydroxy lactam LIV in benzene solution furnished the 5,15-amido ether LII in high yield. This is a key step in the synthesis since it provides us with a compound which is functionalized in the bridging ring.

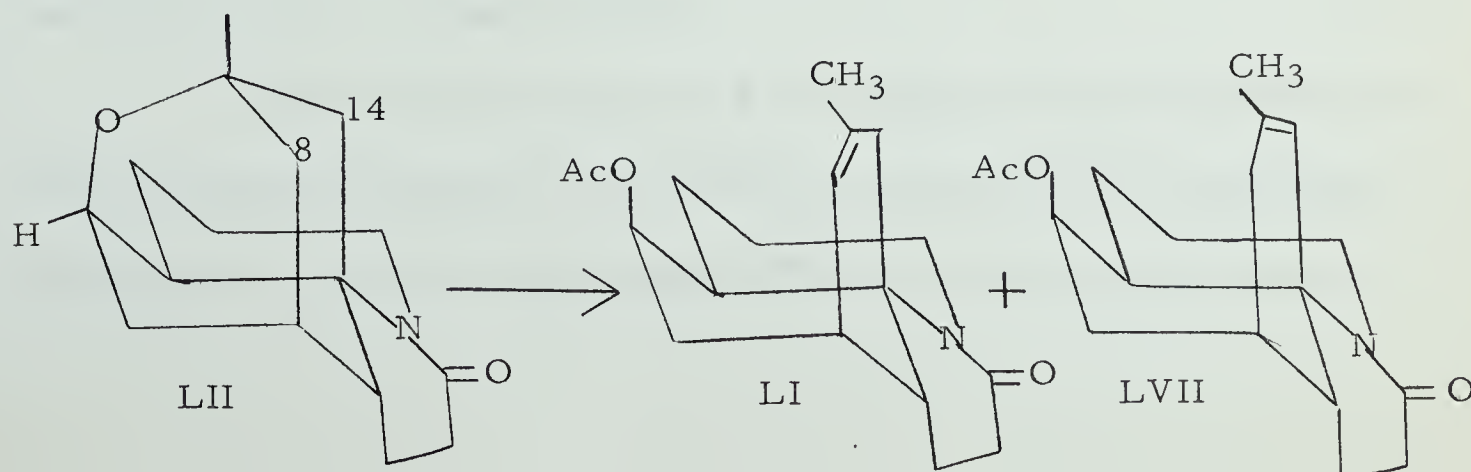
Since oxidation of lycopodine (I) to the corresponding lactam LIII occurred in such low yield other methods of oxidation were investigated. However, neither oxidation of lycopodine (I) with iodine (29) nor with permanganate in aqueous *t*-butanol (30) furnished any of the α -lactam LIII. In both cases, in addition to recovery of starting material, the neutral materials obtained appeared to be over oxygenated as indicated by infrared absorption at 3600 cm^{-1} , 1770 cm^{-1} , 1720 cm^{-1} and 1640 cm^{-1} . The best yield (approximately 45% based on recovered starting material) of the lactam LIII was obtained by oxidation of

lycopodine (I) with neutral potassium permanganate in acetone at room temperature.

Having obtained the 5,15-amido ether LII, it was now necessary to cleave the ether linkage with retention of unsaturation in the bridging ring. The cleavage of ethers with boron trifluoride-etherate in acetic anhydride has been described (27). In this way Ringold and co-workers (27) have cleaved the steroidal oxide LV to the corresponding tetraacetate LVI. While cleavage of primary-



secondary (27) or di-secondary ethers usually leads to the corresponding diacetate, it was felt that in our case, with the tertiary, secondary ether LII, the unsaturated secondary acetate would be obtained. Since there is little reason to expect that proton loss from C-8 would be favored over proton loss from C-14, two different unsaturated acetates, LI and LVII, were expected from cleavage of the 5,15-amido ether LII. Oxygenation at C-8 could then be achieved by using either of the two



olefins (for example, epoxidation or Brown hydration of LI, allylic oxidation of LVII).

When a dilute ethereal solution of the ether LII was treated with boron trifluoride-etherate and acetic anhydride a single product was obtained in good yield. Purification by column chromatography yielded a colorless crystalline compound which showed a single spot on thin layer chromatography.

The mass spectrum of the product showed a parent peak at m/e 303 with the base peak occurring at m/e 243 (M-60), which is in agreement with the formation of either of the expected unsaturated acetates LI or LVII.

The presence of infrared absorption at 1720 and 1240 cm^{-1} , in addition to the lactam band at 1615 cm^{-1} , confirmed the presence of an acetoxyl function. It was now necessary to establish the presence of an olefinic double bond and then to locate the position of the unsaturation.

Hydrolysis of the acetate in aqueous hydrobromic acid reconverted it to the 5,15-amido ether LII in quantitative yield, demonstrating that no major skeletal rearrangement had taken place during the ether cleavage reaction.

That we had in hand the 8,15-unsaturated amido acetate LI was demonstrated clearly by the N.M.R. spectrum of the compound. In addition to a three proton singlet at τ 8.07 for the acetoxymethyl

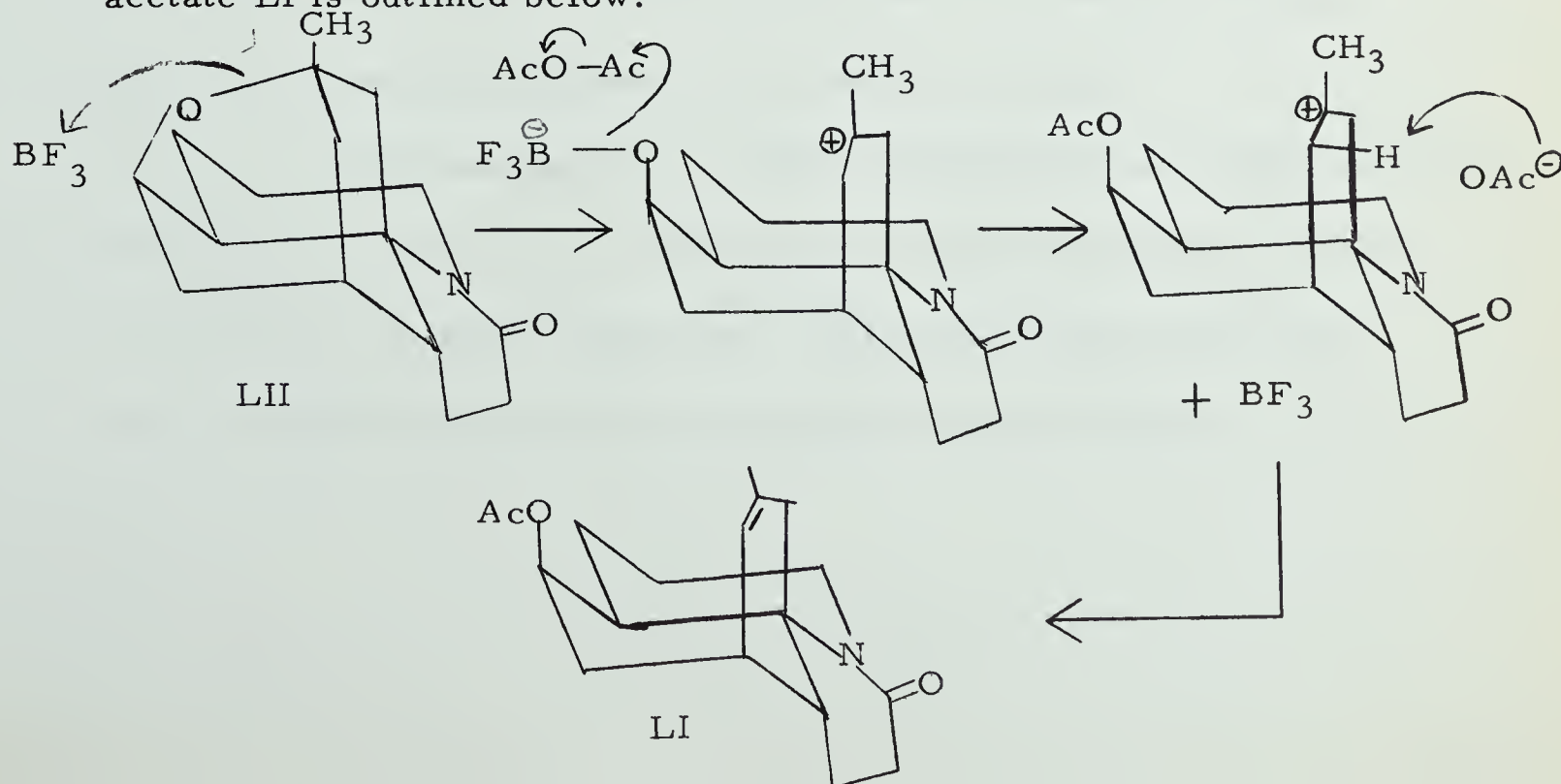
group and a one proton signal at τ 5.15 for the proton on the carbon bearing the acetoxy group, the N.M.R. spectrum contained a slightly broadened three proton singlet at τ 8.32 for the allylic C-15 methyl group as well as a one proton olefinic signal at τ 4.44 which appeared as a broadened doublet with coupling constant $J \approx 6$ cps. The relatively large size of this coupling constant is in good agreement with a 1,2-vicinal coupling which is to be expected from the $\Delta^{8(15)}$ -olefin LI. The size of the coupling constant excludes the presence of the $\Delta^{14(15)}$ -olefin LVII since this compound would show only small 1,3-allylic coupling which normally is no larger than two cps (45, 46).

Double irradiation experiments firmly established the location of the double bond. Irradiation of the methyl group at τ 8.32 converted the olefinic signal to a doublet ($J \approx 6$ cps) of triplets ($J \approx 1.5$ cps). This is consistent with large coupling of the olefinic proton to one adjacent vicinal proton and small coupling to two 1,3-allylic protons. Simultaneous irradiation at τ 8.32 and 8.04 converted the olefinic signal to a doublet ($J \approx 6$ cps) of doublets ($J \approx 1.5$ cps) consistent with coupling of the olefinic proton to one adjacent vicinal proton and now only one allylic proton. Irradiation at τ 8.32 and τ 7.16 again collapsed the olefinic signal to a doublet ($J \approx 6$ cps) of doublets ($J \approx 2$ cps) due to coupling of the olefinic proton with one adjacent vicinal proton and now presumably the other allylic proton. Irradiation at τ 8.32 and τ 7.69 collapsed the olefinic signal to a slightly broadened triplet ($J \approx 1.5$ cps) consistent with

coupling now to only two allylic protons. Simultaneous irradiation at τ 8.04 and τ 7.69 collapsed the olefinic proton to a broadened doublet ($J=1.5$ cps). The above experiments confirm that the olefinic proton is coupled to one adjacent vicinal proton which appears at τ 7.69 with a coupling constant of 6 cps and thus we may definitely assign structure LI to the unsaturated amido acetate.

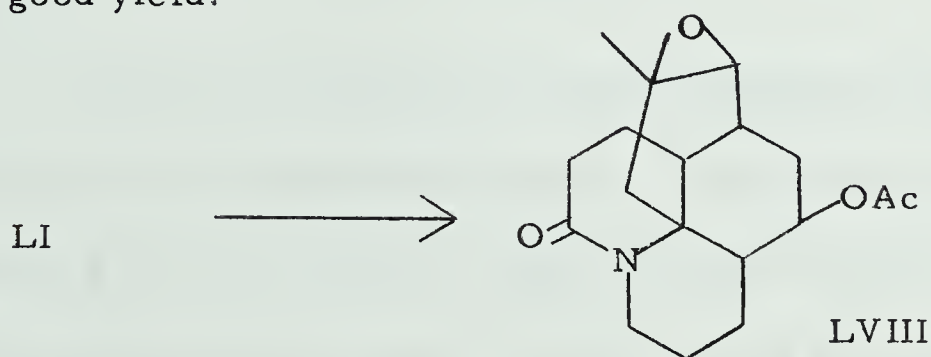
The exclusive formation of only one of the two possible unsaturated acetates is difficult to rationalize. A possible explanation is that the C-8 proton may be less sterically hindered to nucleophilic attack than the C-14 proton.

Another, and perhaps more important reason, for the exclusive formation of only one of the two possible olefins is that the olefin LI may be the thermodynamically favored product because of the proximity of the electron-withdrawing amido group to the Δ^{14} -olefin. One scheme for the formation of the unsaturated amido acetate LI is outlined below.



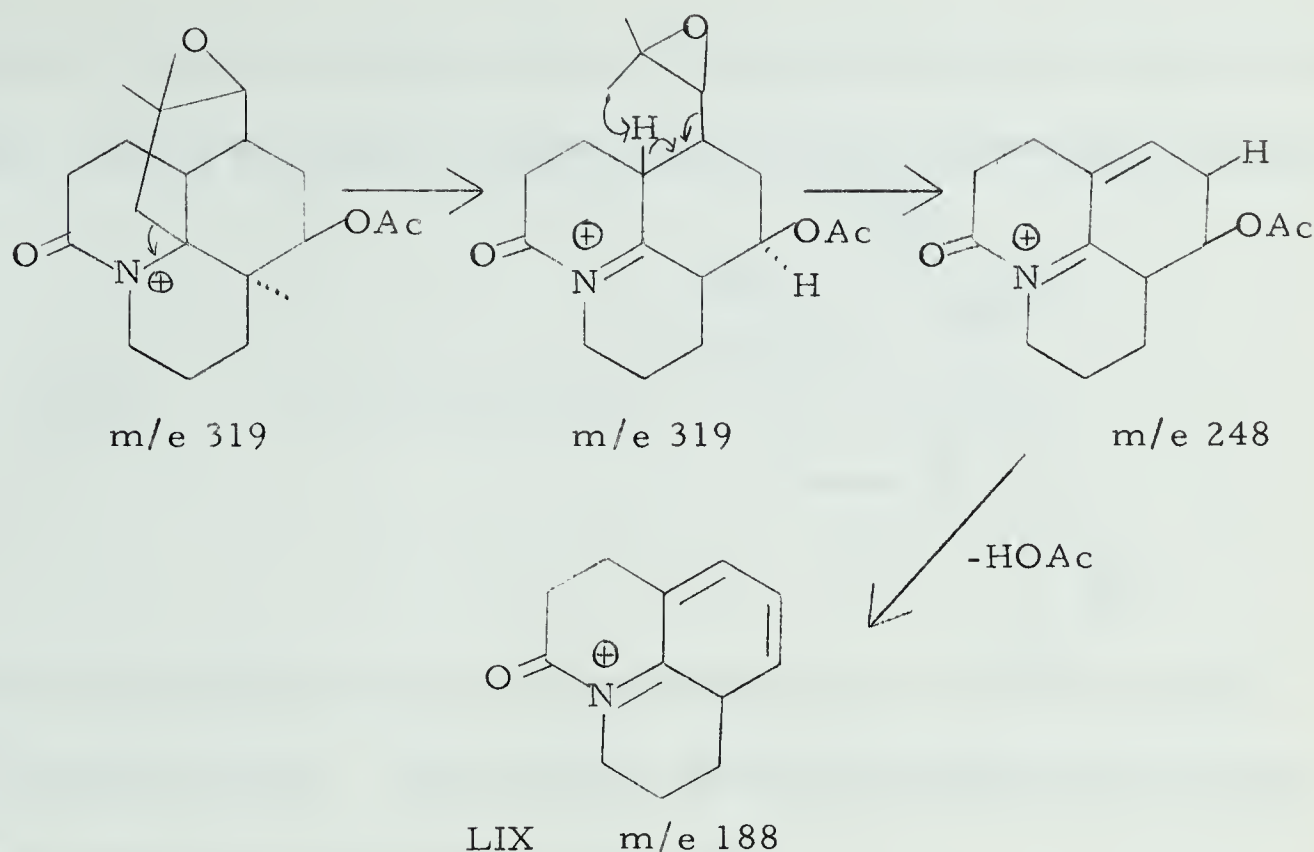
Attempted cleavage of the ether LII in refluxing acetic anhydride containing sodium acetate resulted in the recovery of starting material, demonstrating that the presence of the more powerful Lewis acid, boron trifluoride, is necessary in order to bring about ether cleavage.

The epoxidation of olefinic compounds with peracids in organic solvents is a well known reaction (31). Treatment of a chloroform solution of the unsaturated amido acetate LI with *m*-chloroperbenzoic acid furnished the 8,15-epoxy-5-acetoxy lactam LVIII in good yield.



The epoxide still contained an acetoxy group as indicated by infrared absorption at 1730 and 1225 cm^{-1} as well as a lactam group as shown by the presence of a band at 1635 cm^{-1} .

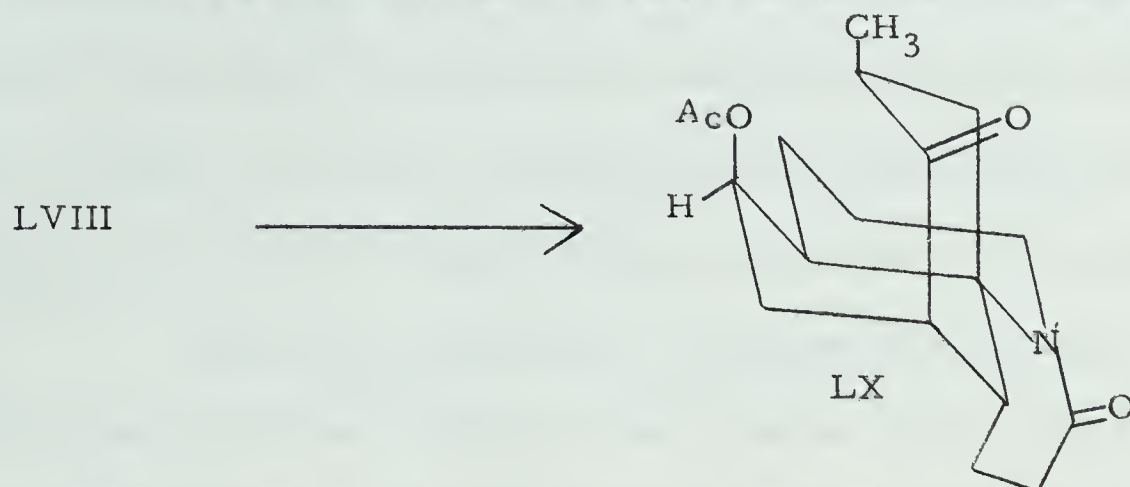
The mass spectrum confirmed that only one oxygen atom had been incorporated into the molecule as the parent peak now occurred at m/e 319. The base peak at m/e 188 is attributed to an ion of structure LIX which could be formed by the scheme shown.



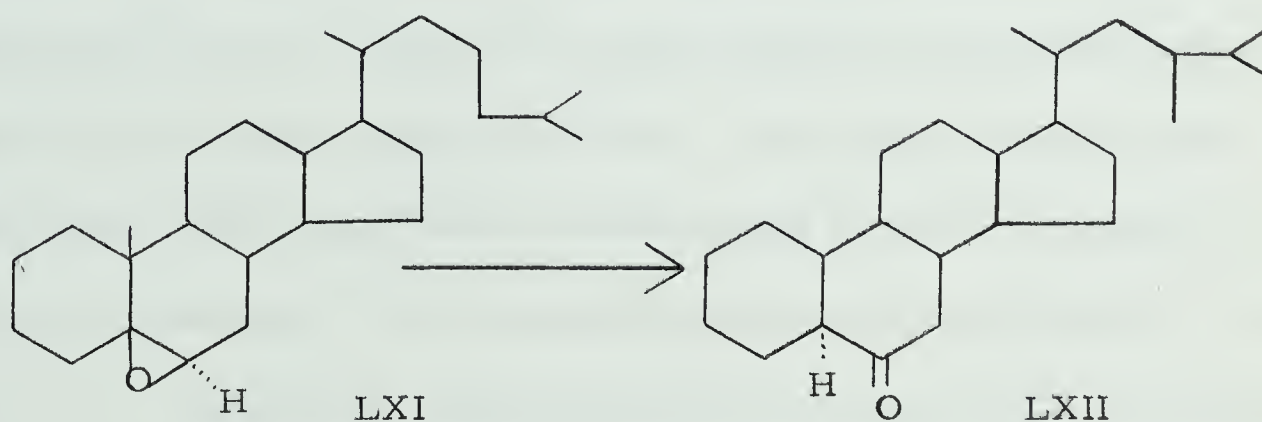
The N.M.R. spectrum of the compound was again useful in showing that the epoxide had formed. The olefinic proton which appeared at $\tau\ 4.44$ in LI was no longer present and the C-15 methyl signal had shifted upfield from $\tau\ 8.32$ in LI to $\tau\ 8.63$ in the epoxide LVIII. This type of upfield shift in the position of the C-15 methyl signal is consistent with the transformation of an olefinic methyl group to a methyl group bonded to a carbon bearing an oxygen function. The C-8 proton now appeared as a doublet ($J=6$ cps) at $\tau\ 7.06$ while the acetoxy methyl signal was at $\tau\ 7.97$ and the C-5 proton appeared at $\tau\ 5.07$. The fact that the C-8 proton appears as a doublet again confirms that the double bond in the olefin was between C-8 and C-15 and not between C-14 and C-15.

It was hoped that rearrangement of the epoxide LVIII with

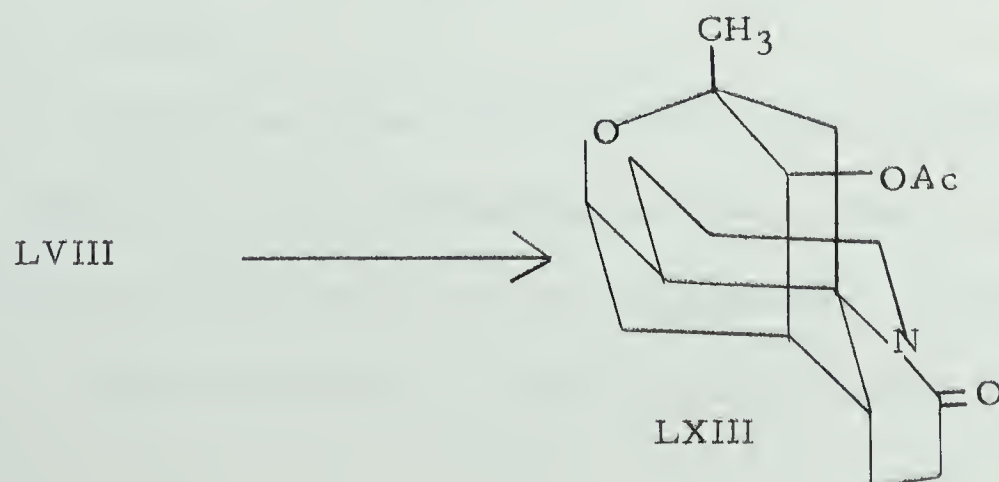
boron trifluoride-etherate (32) would yield the 8-keto-5-acetoxy lactam LX. In this way Henbest and Wrigley (32) have isomerized a variety of



steroidal epoxides to the corresponding ketones via stereospecific 1,2-hydride shifts. For example, 5 β :6 β -epoxycholestane LXI has been isomerized to cholestan-6-one LXII.



However treatment of the 8,15-epoxide LVIII with boron trifluoride-etherate in benzene failed to yield the expected ketone LX. Instead, the 8-acetoxy-5,15-ether LXIII was formed in nearly quantitative



yield. The same product was obtained on reaction of the epoxide LVIII with boron trifluoride-etherate in ether as well as on treatment of a benzene solution of the epoxide with gaseous boron trifluoride. That the 8-acetoxy-5,15-ether LXIII and not the expected ketone LX had formed was indicated by spectral data and confirmed by chemical means.

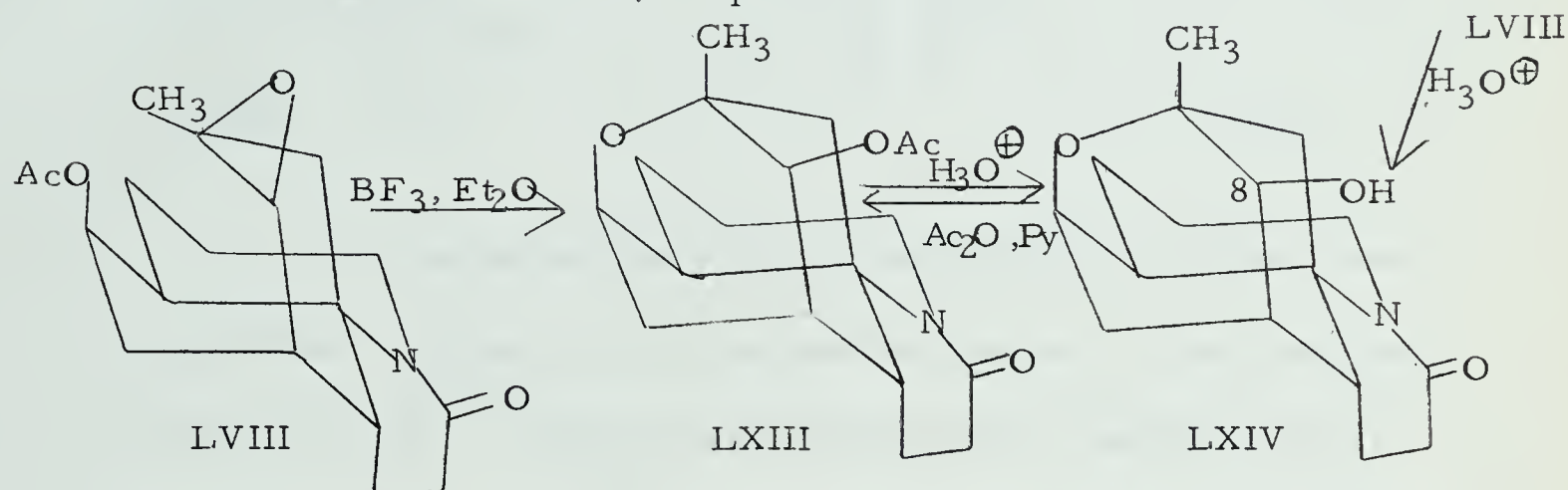
The infrared spectrum of the product contained acetoxyl absorption at 1735 and 1220 cm^{-1} and a lactam band at 1630 cm^{-1} . No keto carbonyl absorption was apparent. Furthermore the optical rotatory dispersion curve did not show a Cotton effect in the $300\text{ m}\mu$ region, confirming the absence of a ketone function. In the N.M.R. spectrum of the 8-acetoxy-5,15-ether LXIII the C-15 methyl signal appeared as a sharp singlet at $\tau 8.85$. One proton signals which appeared at $\tau 5.3$ and $\tau 6.42$ are attributed to the C-8 and the C-5 proton respectively. The acetoxy methyl signal occurred at $\tau 7.92$.

Hydrolysis of the 8-acetoxy-5,15-ether LXIII with aqueous hydrobromic acid furnished the corresponding 8-hydroxy-5,15-ether LXIV. The hydroxy compound was void of infrared absorption in the $1700\text{-}1800\text{ cm}^{-1}$ region and revealed bands at 3610 cm^{-1} (hydroxyl) and 1605 cm^{-1} (lactam).

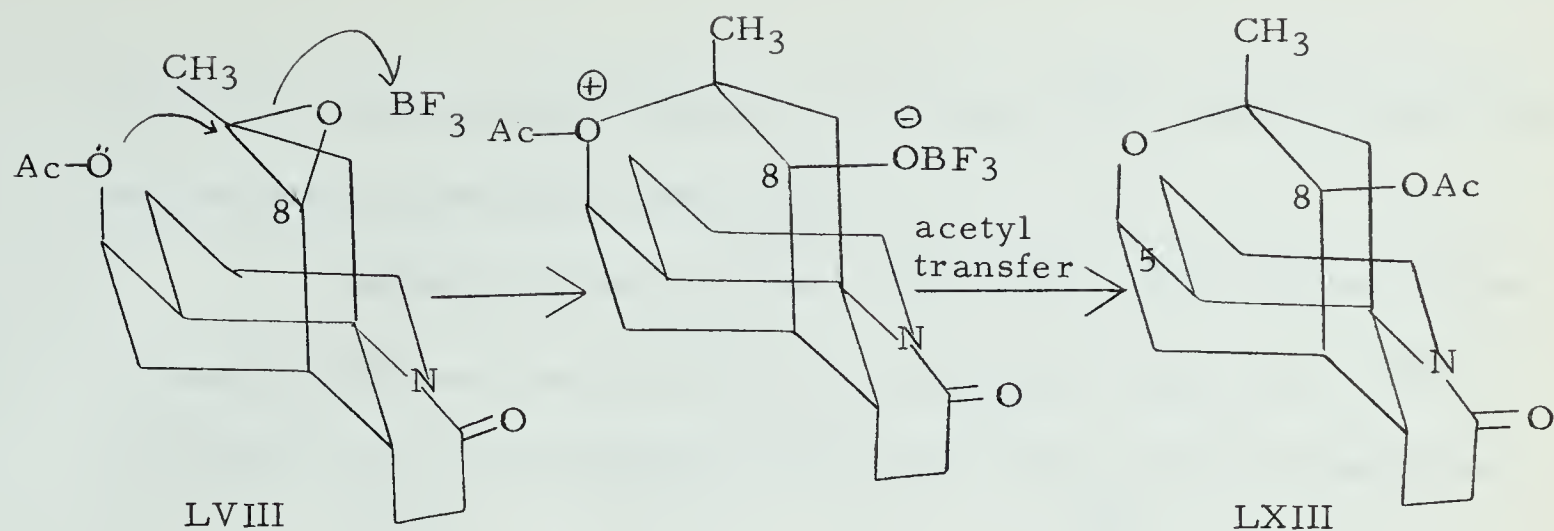
Acetylation of the 8-hydroxy-5,15-ether LXIV regenerated the 8-acetoxy-5,15-ether LXIII indicating that no skeletal rearrangement had taken place on hydrolysis of the acetoxyl function present in LXIII.

Reaction of the 8,15-epoxy-5-acetoxy lactam LVIII with

aqueous hydrobromic acid yielded the expected 8-hydroxy-5,15-ether LXIV directly. These reactions, summarized in the equations below, confirm the structure of the product obtained from boron trifluoride-etherate treatment of the 8,15-epoxide LVIII.



The facile formation of the acetate LXIII on reaction of the epoxide XLIV with boron trifluoride-etherate, though unexpected, is readily rationalized. Presumably the reaction proceeds by Lewis acid catalyzed opening of the epoxide ring toward the more stable tertiary carbonium ion. This reaction may occur with simultaneous participation of the C-5 acetoxyl group, thus stabilizing the carbonium ion being formed. Because of the axial orientation of the acetoxyl function such participation is not unexpected since the ethereal oxygen of the acetoxyl group and the C-15 carbon are in close proximity to one another. Then either intra- or inter- molecular transfer of the acetyl group from the C-5 oxygen to the C-8 oxygen would yield the 8-acetoxy-5,15-ether LXIII.



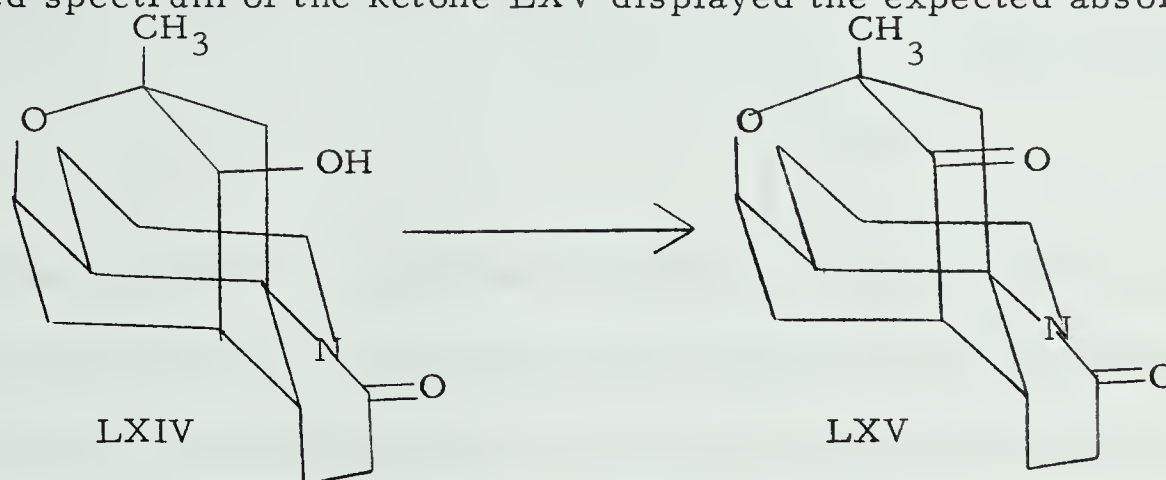
It must be pointed out that this series of reactions does not establish definitely the stereochemistry at the C-8 carbon atom in LXIII and LXIV. The stereochemistry of the epoxide is very likely that shown in LVIII since it would be expected to be formed by attack from the less hindered side of the olefin LI. The N.M.R. spectrum of the acetate LXIII was of little help in assigning the stereochemistry at this center since the proton at C-8 which appeared at τ 5.3 was present as a very broad singlet. We favor the stereochemistry shown in LXIII on the basis of a trans diaxial opening of the epoxide ring in LVIII resulting from backside attack of the axial C-5 oxygen on C-15. If the stereochemistry at C-8 is as shown then transfer of the acetyl group from the C-5 to C-8 oxygen function probably takes place by an intermolecular process.

Presumably a similar type of mechanism obtains in the transformation of the epoxide LVIII into the 8-hydroxy-5,15-ether LXIV on treatment with aqueous hydrobromic acid.

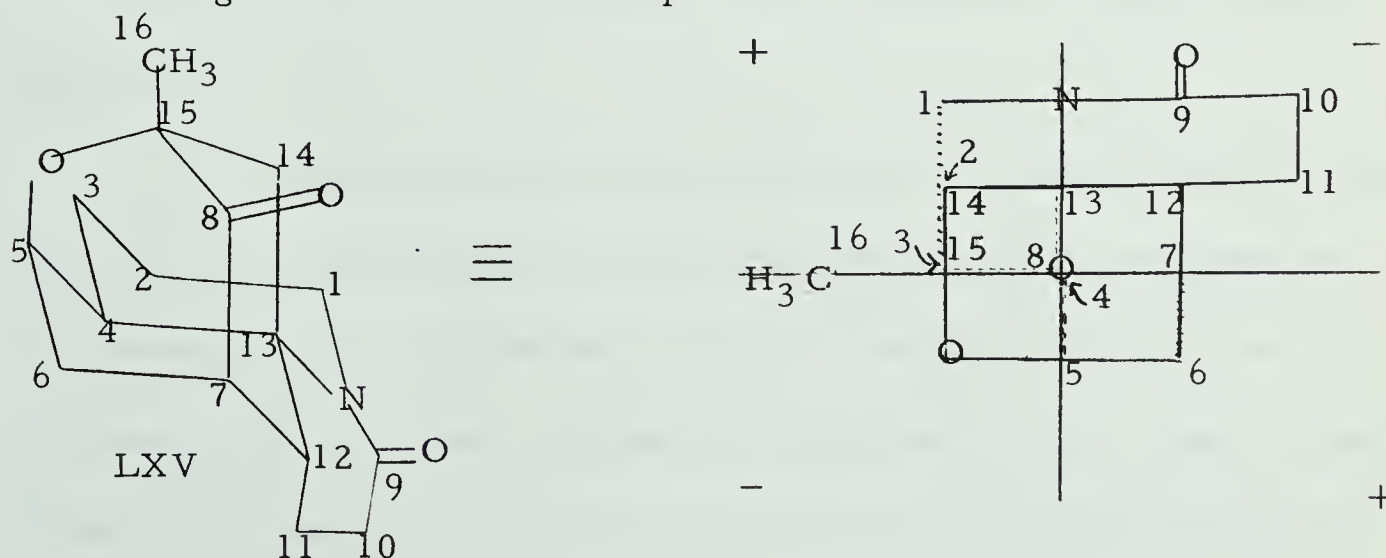
Although the desired 8-keto-5-acetoxy lactam LX was not

obtained we felt that the 8-hydroxy-5,15-ether LXIV could be transformed into the 8-keto-5-acetoxy lactam LXV.

Oxidation of the 8-hydroxy-5,15-ether LXIV with chromium trioxide in 95% acetic acid gave the corresponding ketone LXV. The infrared spectrum of the ketone LXV displayed the expected absorption

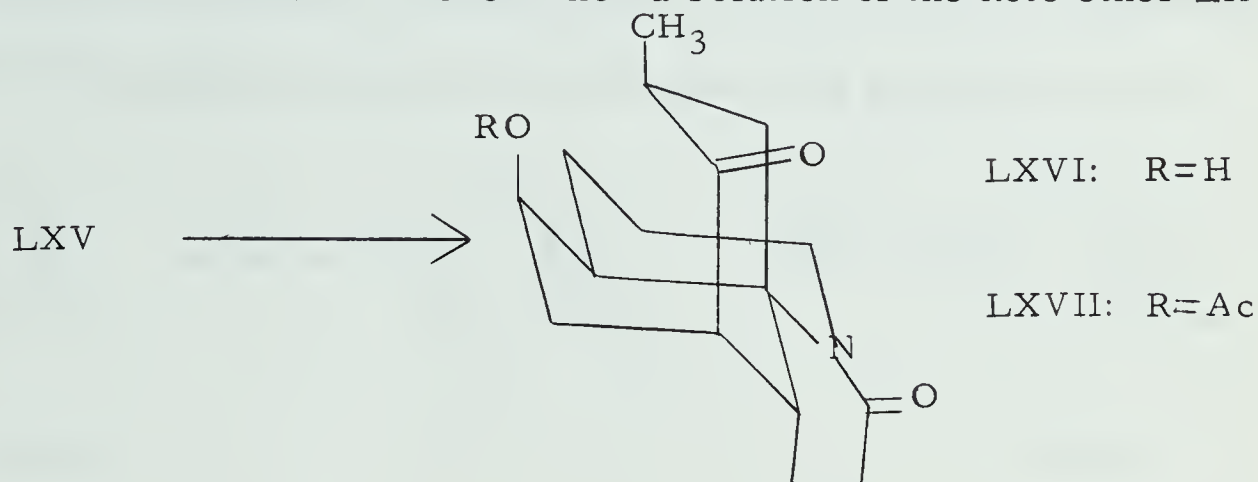


bands at 1720 cm^{-1} and 1620 cm^{-1} . The optical rotatory dispersion curve showed a negative Cotton effect (39) with extrema at 319 and 282 $m\mu$, amplitude $[\phi] -2650^\circ$. On the basis of the octant diagram shown below a negative Cotton effect is predicted for the ketone LXV.



The use of calcium in liquid ammonia for the reduction of α -hydroxy or α -acetoxy ketones to the corresponding ketones has been described (40). We felt that in the case of the α -alkoxy ketone LXV,

calcium-ammonia reduction perhaps could give us the desired 5-hydroxy-8-keto lactam LXVI. However when a solution of the keto ether LXV

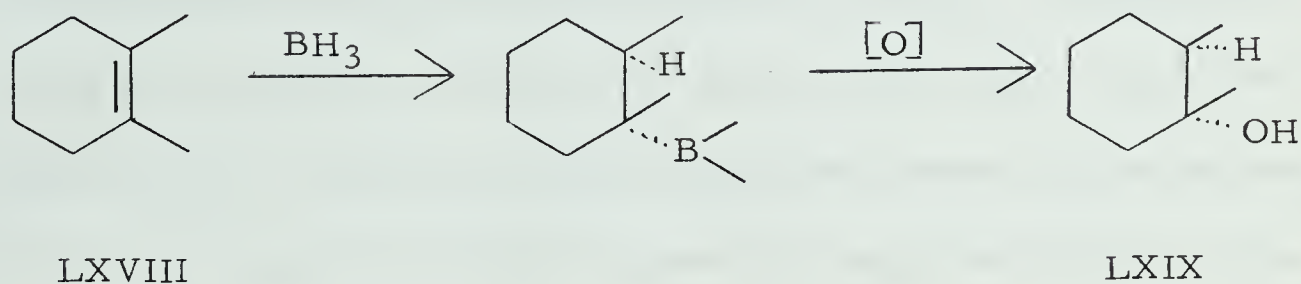


in toluene was added to a solution of calcium in liquid ammonia the product obtained was an intractable gum which did not show hydroxyl absorption in the infrared spectrum and hence probably had not been reduced in the desired direction. The material was not further characterized.

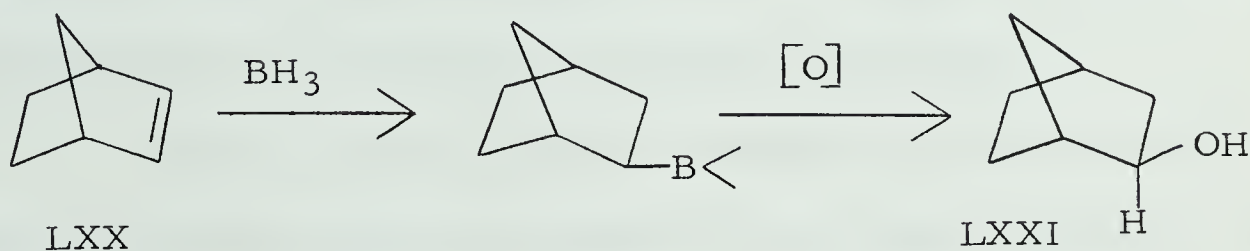
Attempted reduction of the keto ether LXV to the corresponding 5-acetoxy-8-keto lactam LXVII with zinc dust in acetic anhydride (41) was also unsuccessful and only starting material was obtained.

Since the preliminary experiments to reduce the keto ether LXV were unsuccessful we decided to investigate other methods for oxygenating the C-8 carbon atom of the unsaturated amido actate LI. The most obvious method of achieving oxygenation at C-8 was via the Brown hydration procedure (42) which proceeds by hydroboration of the olefin followed by alkaline oxidation of the intermediate borane to the corresponding alcohol. The reaction results in overall cis addition of water in an anti-Markovnikoff fashion from the least hindered

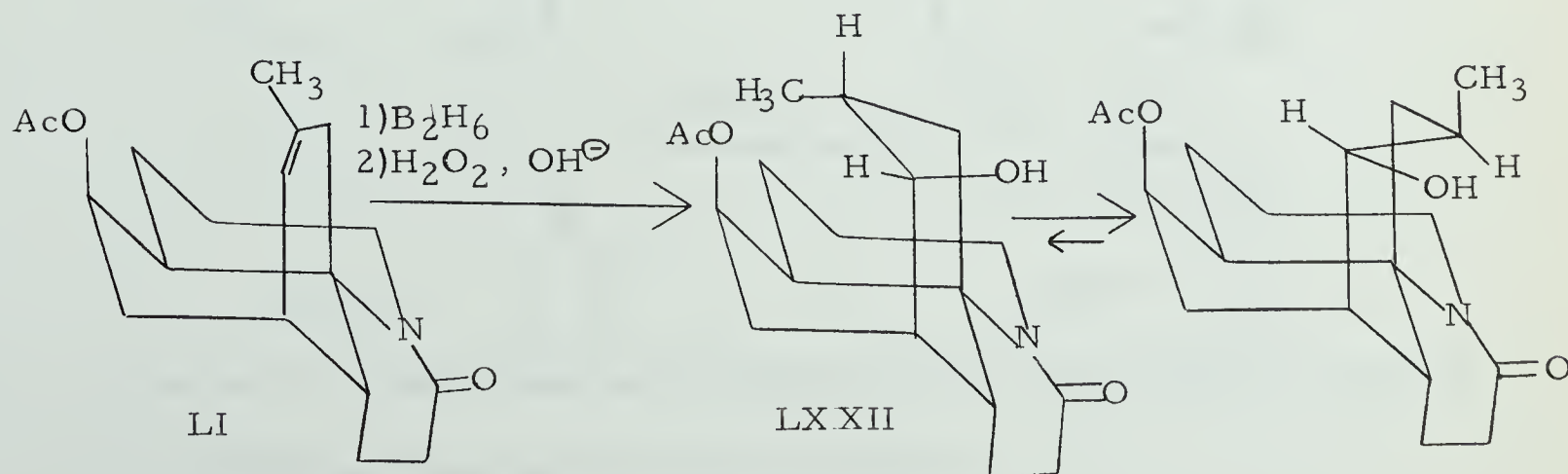
side of the molecule (43). Thus, for example, Brown hydration of 1,2-dimethylcyclohexene LXVIII yields *cis*-1,2-dimethylcyclohexanol LXIX (42) and hydroboration of norbornene LXX proceeds to give



exo-norborneol LXXI almost exclusively (42), the result of *cis* addition of water from the less hindered side of the molecule.



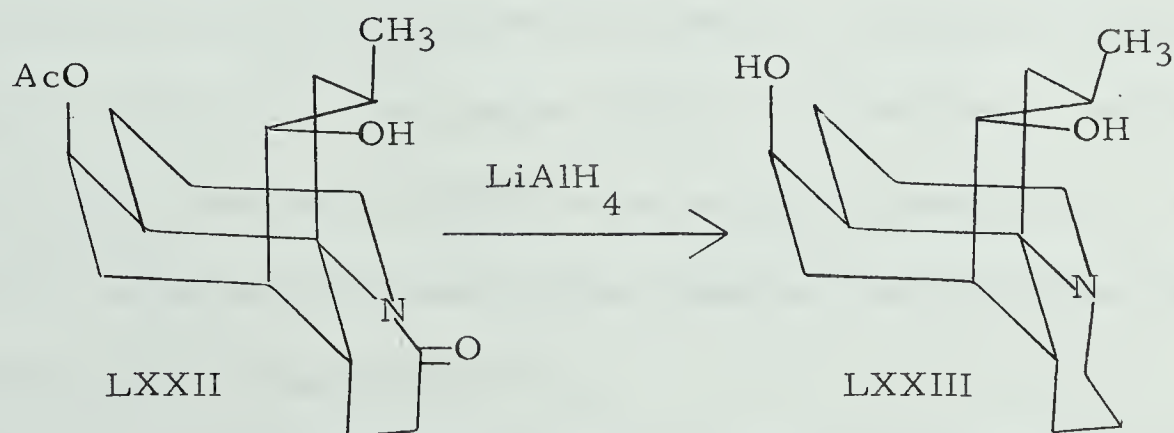
On the basis of the above evidence hydroboration of the unsaturated amido acetate LI was expected to yield the corresponding 8-hydroxy-5-acetoxy lactam LXXII with the stereochemistry as shown resulting from addition of diborane to the less hindered side of the



double bond.

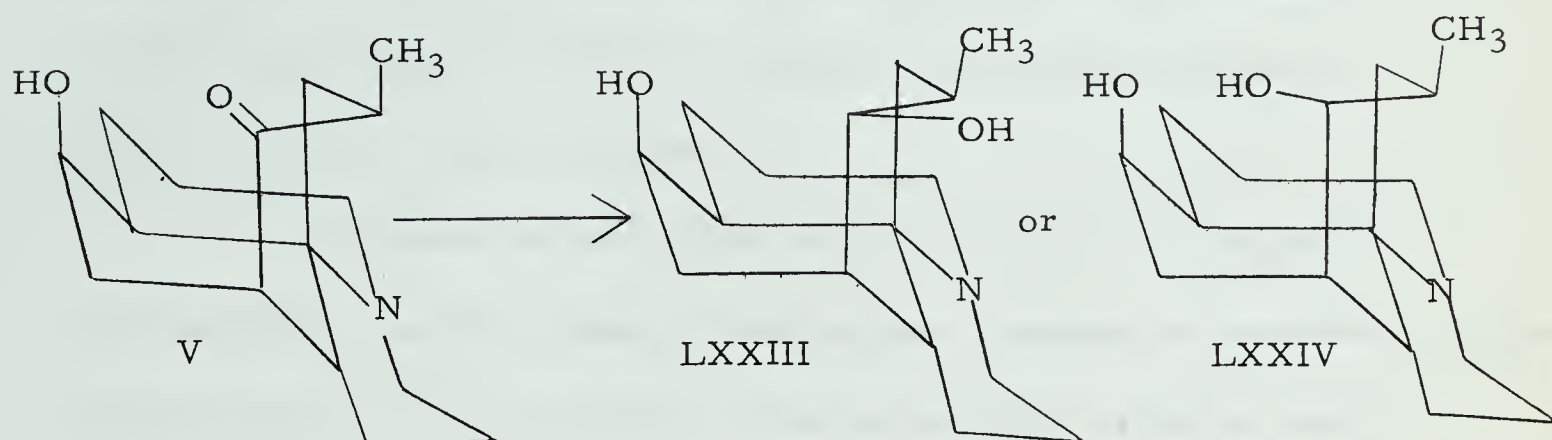
Indeed when the olefin LI was treated with excess diborane at room temperature for forty-five minutes followed by oxidation in alkaline peroxide the alcohol LXXII was formed in good yield. Broad strong infrared absorption (Nujol mull) at 3350 cm^{-1} , in addition to acetate bands at 1730 and 1240 cm^{-1} and a lactam band at 1610 cm^{-1} , confirmed that a hydroxyl group had been introduced into the molecule. The N.M.R. spectrum of the compound no longer had signals in the olefinic region and the C-15 methyl group now appeared as a doublet ($J=6$ cps) at $\tau 8.87$. The acetate methyl group appeared at $\tau 7.93$ (singlet) and the one proton signals at $\tau 6.41$ ($W_{1/2}=12$ cps) and $\tau 5.04$ were attributed to the C-8 and C-5 protons respectively.

Before going on with the synthesis of annofoline (V) an effort was made to obtain a correlation of the "synthetic" series with the naturally occurring series. The 8-hydroxy-5-acetoxy lactam LXXII was reduced with excess lithium aluminum hydride to give the basic diol LXXIII, mp $260-261^{\circ}\text{C}$. The infrared spectrum of the diol LXXIII



was devoid of absorption in the carbonyl region and contained a strong broad hydroxyl band at 3400 cm^{-1} in Nujol.

It has been shown (17) that lithium aluminum hydride reduction of annofoline (V) gives only one product, α -dihydroannofoline, which should have either structure LXXIII or LXXIV. If α -dihydroannofoline has structure LXXIII it should be identical with the synthetic



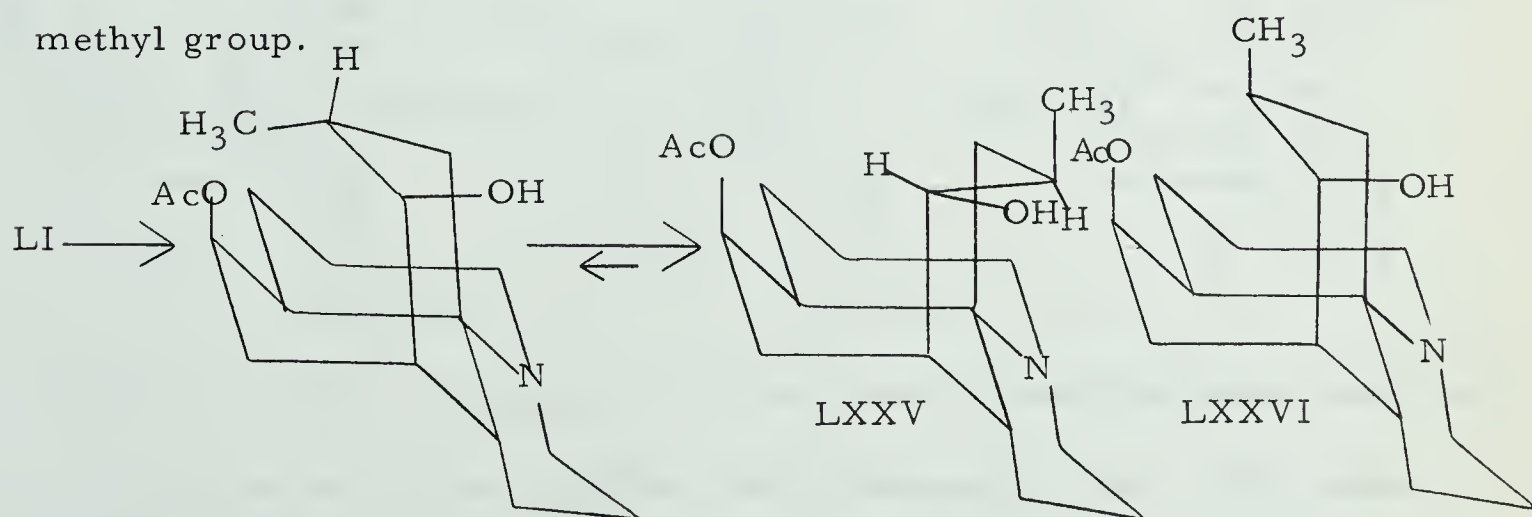
product obtained by lithium aluminum hydride reduction of the 8-hydroxy-5-acetoxy-lactam LXXII.

When we reduced annofoline (V) with lithium aluminum hydride a high yield of α -dihydroannofoline was obtained, mp 264-265°C. This material proved to be non-identical with the synthetic diol LXXIII (infrared spectrum, mixed melting point was strongly depressed) and hence, if the stereochemical assignment made for the synthetic diol LXXIII is correct, then the stereochemistry of α -dihydroannofoline must be that shown in structure LXXIV. That α -dihydroannofoline should have structure LXXIV, is not surprising since this is the product expected from attack of the reducing agent from the least hindered side of annofoline (V).

Examination of the mother liquors from the recrystallization of α -dihydroannofoline by thin layer chromatography revealed the presence

of two components. The faster running of these had the same R_f -value as α -dihydroannofoline and the slower running component had the same R_f as the synthetic basic diol LXXIII. Presumably in the lithium aluminum hydride reduction of annofoline (V) the major product is α -dihydroannofoline (LXXIV) but a small amount of the epimeric alcohol LXXIII is also produced.

Returning to the synthesis of annofoline (V), treatment of the unsaturated amido acetate LI with excess diborane at room temperature for about three hours followed by alkaline peroxide oxidation gave a basic product which no longer contained a lactam function as indicated by the infrared spectrum. Purification by recrystallization gave the pure hydroxy acetate LXXV which we have named 15-epilofoline since it presumably is epimeric to lofoline LXXVI (17, 43) at the C-15 methyl group.

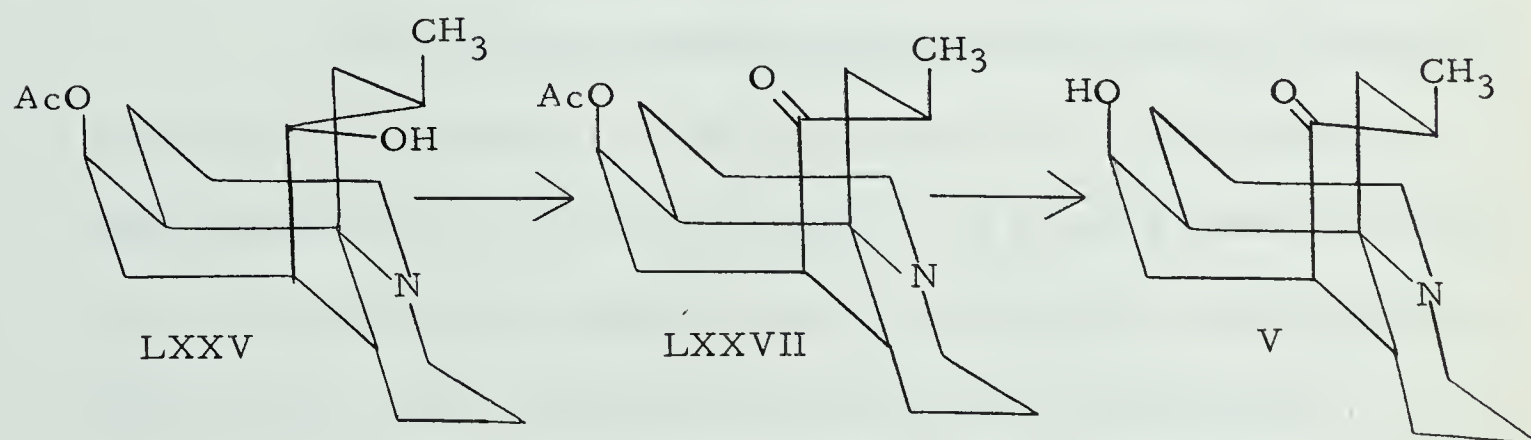


15-Epilofoline (LXXV) revealed infrared bands in chloroform at 3605 cm^{-1} (hydroxyl) and 1730 cm^{-1} (acetoxyl) and the N.M.R. spectrum displayed signals at $\tau 8.9$ (3H, doublet, $J=5$ cps) for the C-15 methyl group, $\tau 7.95$ (3H, singlet) for the acetoxy methyl, and one proton

multiplets at τ 6.46 ($W_{1/2} = 12$ cps) and τ 5.01 due to the C-8 and C-5 proton respectively.

The reduction of the lactam group during the hydroboration of the olefin LI was unexpected since at the time that this experiment was done no literature examples reporting the reduction of amides or lactams with diborane could be found. However after this work had been completed, Brown and Heim (44) reported the reduction of a variety of amides to the corresponding amines with diborane in refluxing tetrahydrofuran.

Oxidation of 15-epilofoline (LXXV) with chromium trioxide-pyridine afforded, after purification by chromatography, O-acetylannofoline (LXXVII) as a pale yellow oil. The synthetic O-acetyl-



annofoline (LXXVII) obtained in this way was identical (infrared spectrum in carbon tetrachloride, optical rotatory dispersion curve, thin-layer chromatographic behavior) with authentic O-acetylannofoline.

Treatment of the synthetic O-acetylannofoline (LXXVII) with methyl iodide gave the corresponding methiodide, identical (infrared spectrum in Nujol, melting point, mixed melting point) with authentic

O-acetylannofoline methiodide kindly provided by Dr. R. H. Burnell.

Finally alkaline hydrolysis of the synthetic O-acetyl annofoline (LXXVII) gave annofoline (V), identical (infrared spectrum in chloroform, thin layer chromatographic behavior) with authentic naturally occurring annofoline (V).

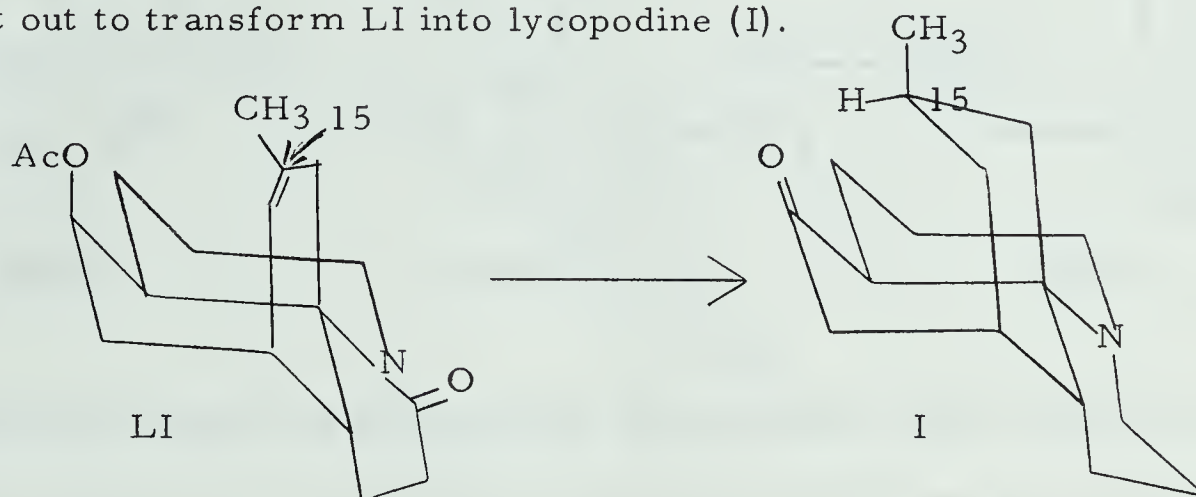
This series of reactions provides a direct chemical correlation of lycopodine with annofoline, and provides a method for the introduction of oxygen functions into the bridging ring in the lycopodine-type alkaloids, a sequence which may have a biosynthetic parallel.

B. THE TRANSFORMATION OF THE UNSATURATED AMIDO ACETATE LI INTO LYCOPODINE (I)

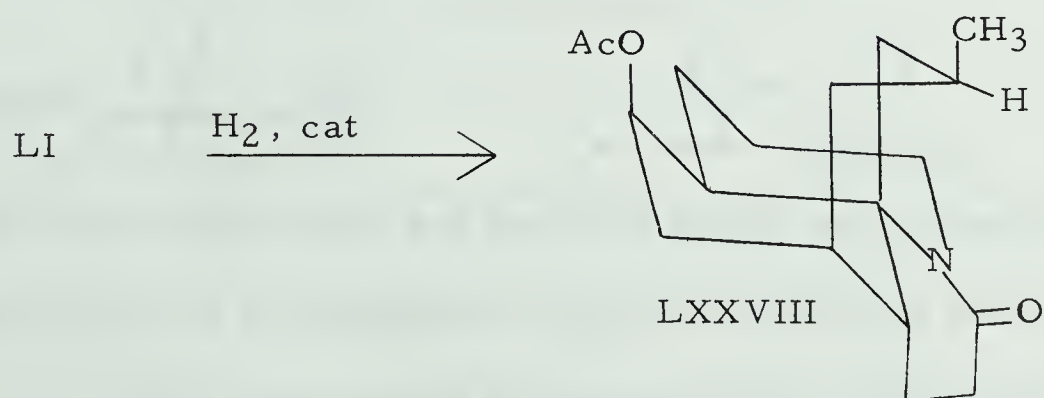
One of the most difficult problems encountered in the total synthesis of a naturally occurring compound is that of controlling the stereochemistry of the synthetic product. In a total synthesis not only must the correct ring skeleton be constructed, but the stereochemistry of the product must be that of the naturally occurring compound.

The total synthesis of the alkaloid lycopodine (I) has not yet been achieved, although different approaches to such a synthesis have already been described (21, 22). In carrying out the total synthesis of lycopodine(I), control of the stereochemistry of the C-15 methyl group poses a potential problem since the ring carrying the methyl group is not functionalized. We felt that the unsaturated amido acetate LI

described in section A, provided a suitable substrate on which to investigate a potential method for the solution of this problem, and set out to transform LI into lycopodine (I).

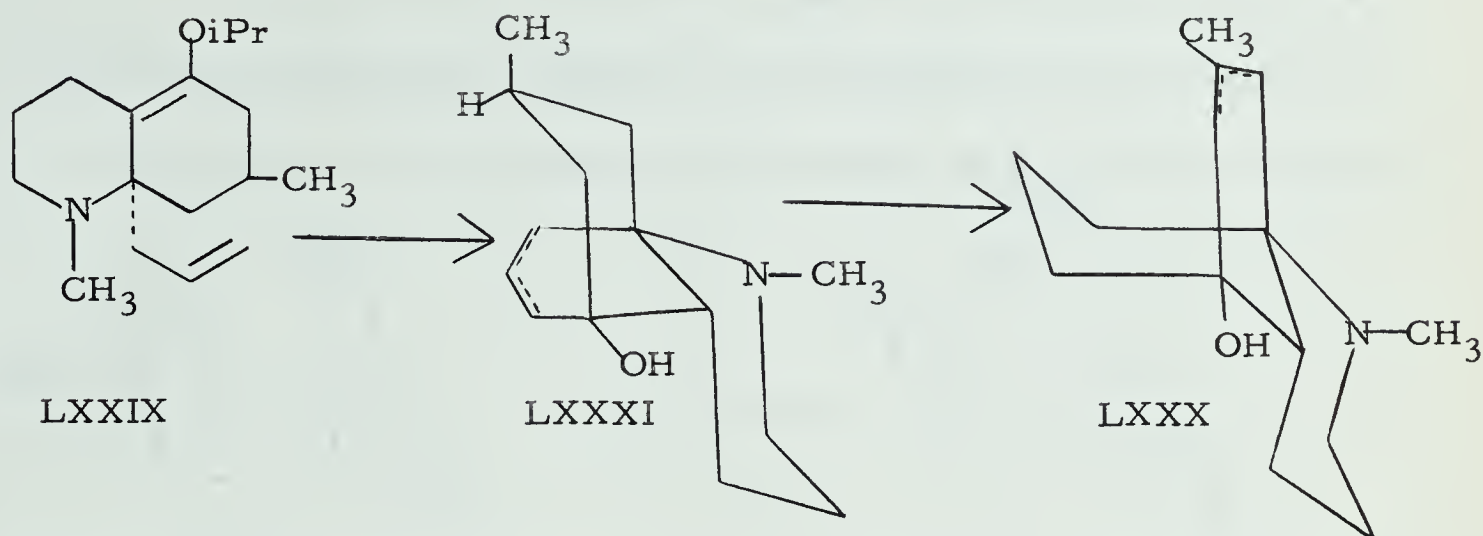


Such a transformation involves the addition of hydrogen to the more hindered side of the double bond in LI. Normal catalytic hydrogenation of the olefin LI would be expected to proceed from the less hindered side of the molecule thus yielding the product LXXVIII which has the opposite stereochemistry at C-15 to that of lycopodine (I).



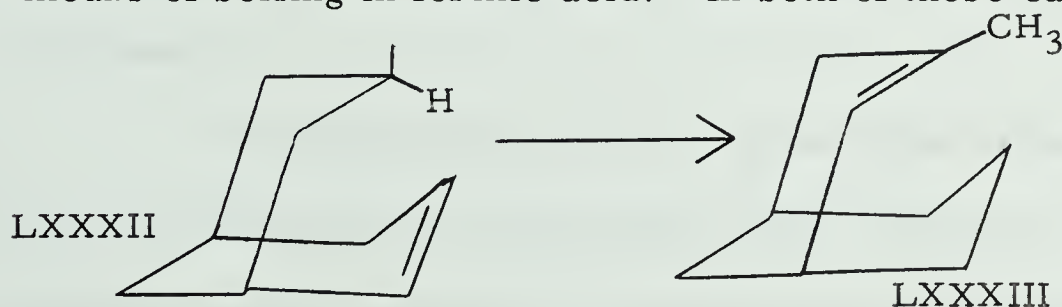
Recently considerable interest has been shown in transannular reactions in the bicyclo [3,3,1] nonane system (21, 47, 48, 49) and the occurrence of transannular hydride shifts in these systems has been reported (21, 49). Thus Wiesner, Valenta and co-workers (21) have reported the transformation of the amine LXXIX into the amine

LXXX by treatment with 70% sulfuric acid. This reaction presumably



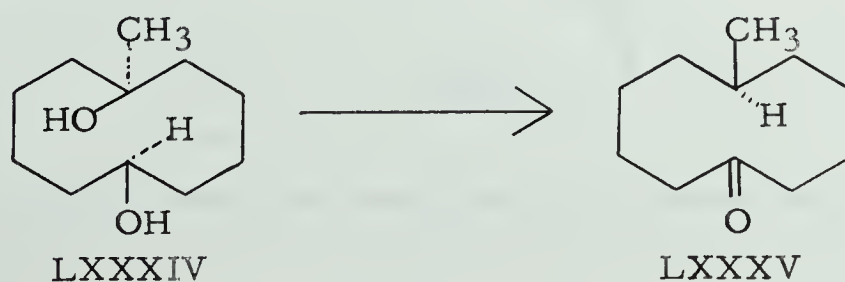
proceeds through the intermediate disubstituted olefin LXXXI which is then isomerized to the trisubstituted olefin LXXX via a transannular hydride shift.

Appleton and Graham (49) have reported the transformation of the disubstituted olefin LXXXII into the trisubstituted olefin LXXXIII by means of boiling in formic acid. In both of these cases the driving

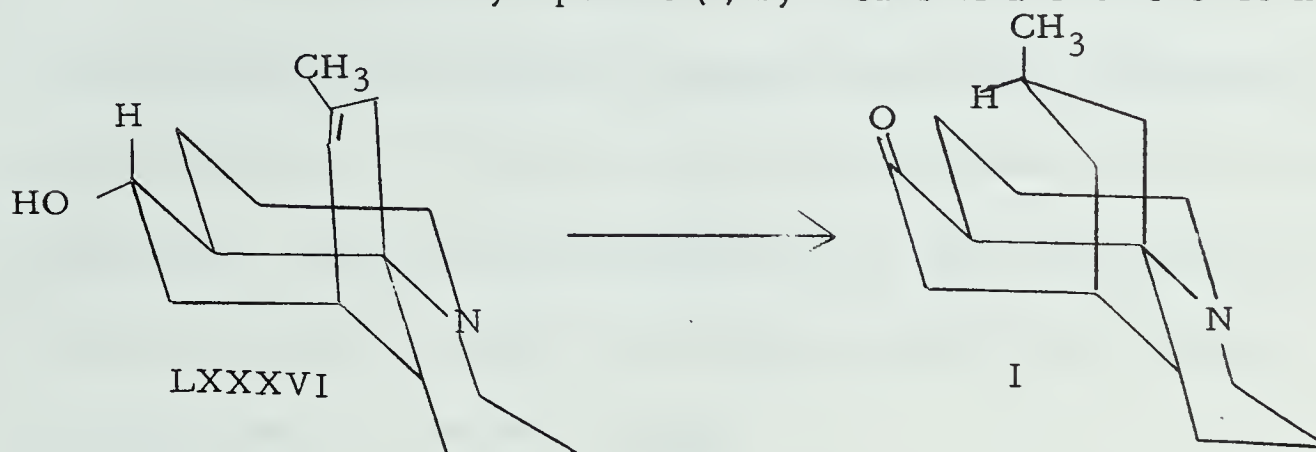


force for the hydride shift has been the energy gain associated with the transformation of a disubstituted into a trisubstituted olefinic system.

The isomerization in strong acids of the secondary alcohol LXXXIV into the ketone LXXXV in the cyclodecane system has been shown (50) to proceed via a transannular hydride shift.

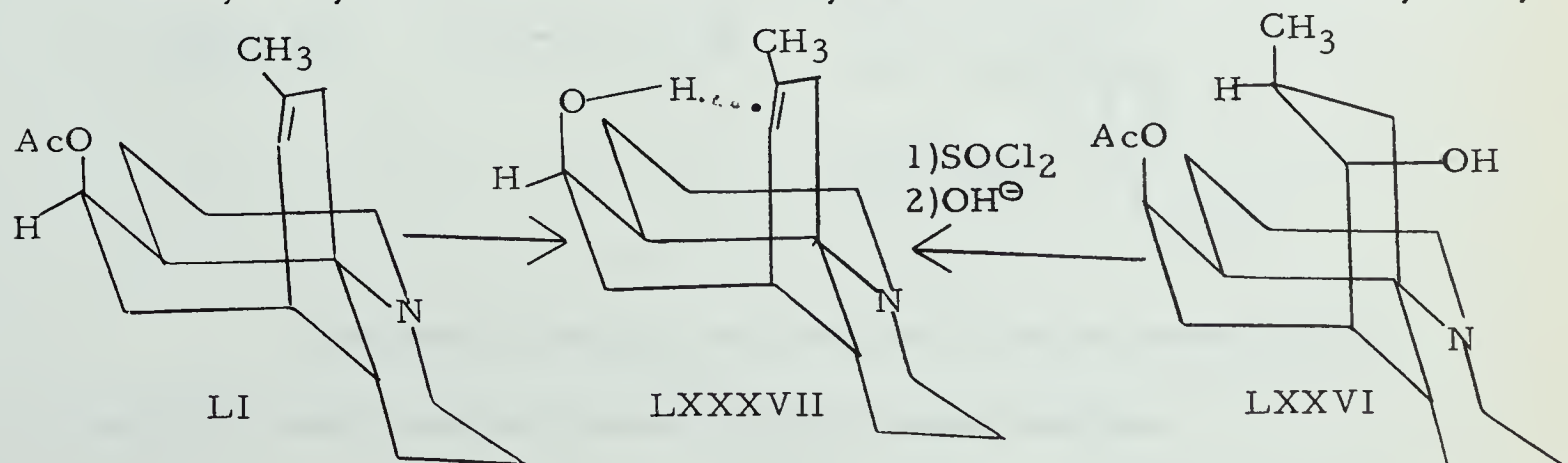


On the basis of the above observations we felt that if we could prepare the alcohol LXXXVI then treatment with a strong acid should isomerize it to lycopodine (I) by means of a C-5 to C-15 hydride



shift with participation of the equatorial C-5 hydroxyl group. This method then would provide a ready means of adding hydrogen to the more hindered side of C-15, thus giving the lycopodine stereochemistry at that center, a result not easily achieved by more conventional procedures.

The starting point for the preparation of the unsaturated alcohol LXXXVI was the unsaturated amido acetate LI. Lithium aluminum hydride reduction of LI gave in almost quantitative yield the basic hydroxy olefin LXXXVII as a crystalline solid. The same hydroxy



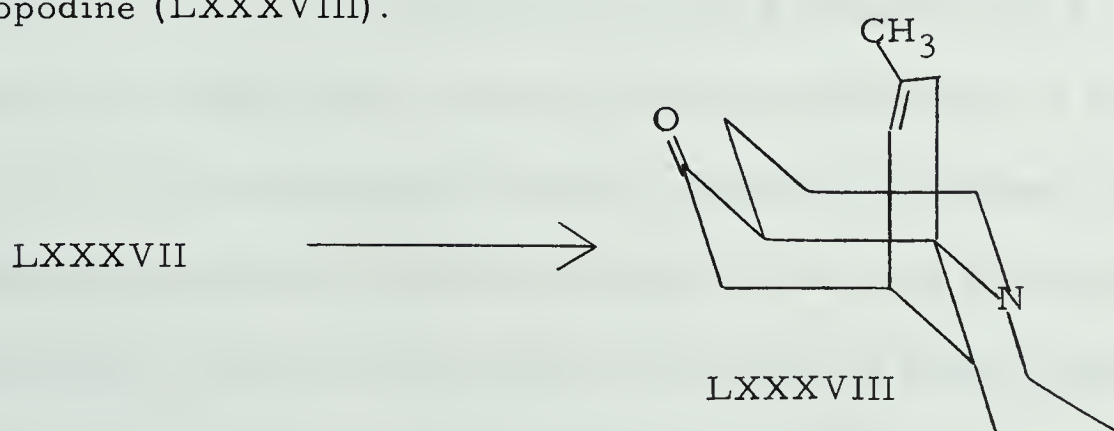
olefin LXXXVII was also obtained by dehydration of lofoline (LXXVI)

with thionyl chloride (36) followed by removal of the acetoxy group by alkaline hydrolysis.

The infrared spectrum of the hydroxy olefin LXXXVII in carbon tetrachloride displayed a sharp concentration independent band at 3542 cm^{-1} . The fact that the hydroxyl absorption is concentration independent confirms the axial nature of the hydroxyl group since in this orientation it is able to undergo intramolecular hydrogen bonding to the 8,15-olefinic linkage.

The N.M.R. spectrum was consistent with the structure assigned to the product LXXXVII as it contained signals for an allylic methyl group at τ 8.3 and it also had a one proton doublet ($J = 6\text{ cps}$) at τ 4.14 for the olefinic proton.

Modified Oppenauer oxidation (51) of the hydroxy olefin LXXXVII gave a high yield of the corresponding ketone, 8,15-dehydrolycopodine (LXXXVIII).

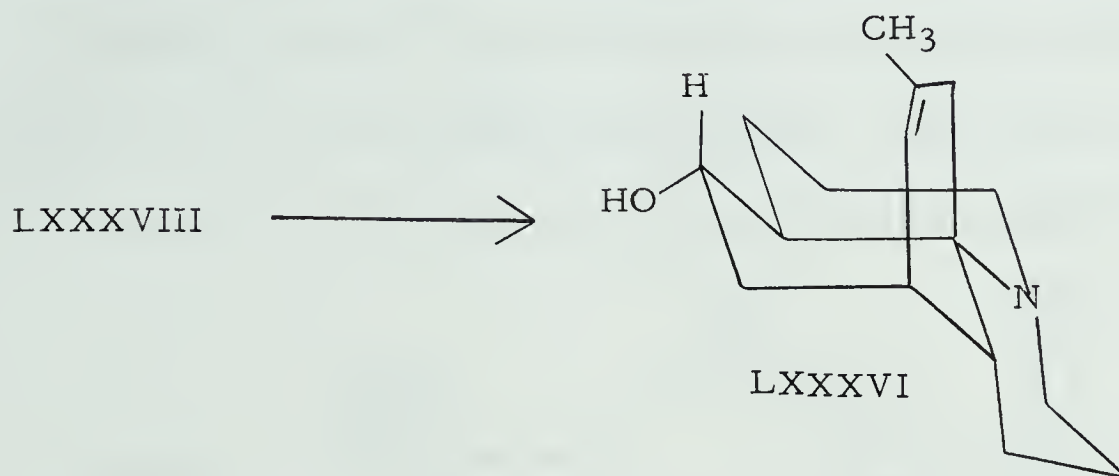


Infrared absorption at 1705 cm^{-1} (carbon tetrachloride solution) confirmed the presence of the ketone function.

The N.M.R. spectrum had a three proton signal at τ 8.40

(broadened singlet) for the allylic C-15 methyl group and a one proton doublet ($J=6$ cps) at τ 4.58 for the olefinic C-8 proton.

Lithium-ammonia-methanol reduction of the ketone LXXXVIII furnished $\Delta^{8(15)}$ - α -dihydrolycopodine (LXXXVI) as an amorphous



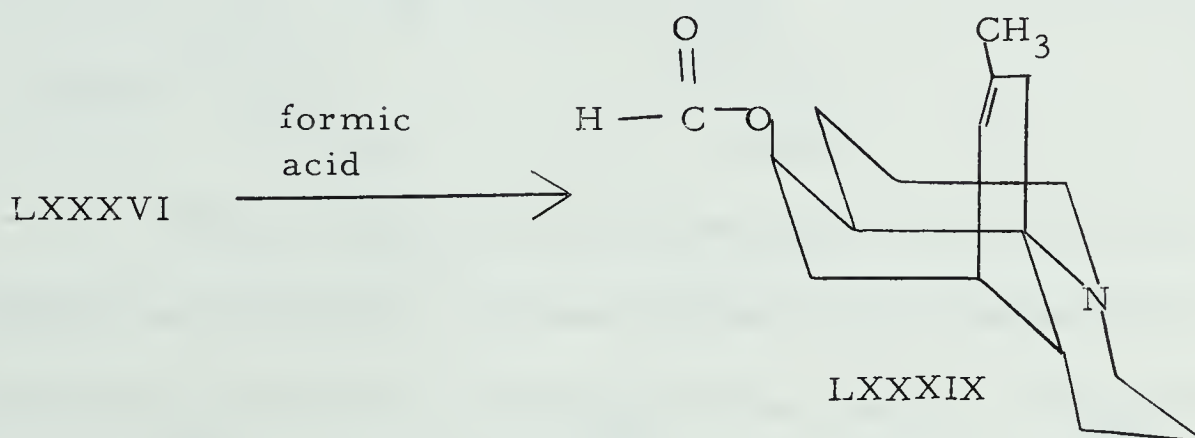
solid which could not be induced to crystallize.

That the equatorial alcohol LXXXVI had formed was confirmed by the infrared spectrum which contained a sharp band at 3610 cm^{-1} in carbon tetrachloride. The fact that the alcohol LXXXIX has a non-hydrogen bonded hydroxyl group, whereas its C-5 epimer LXXXVII has a strongly intramolecularly hydrogen bonded hydroxyl, demonstrates that in the alcohol LXXXVI, the hydroxyl is equatorial.

The unsaturated system present in the ketone LXXXVIII was unaffected during the lithium-ammonia reduction as demonstrated by the N.M.R. spectrum which contained an allylic methyl signal at τ 8.35 and a vinylic proton as a doublet ($J=6$ cps) at τ 4.5.

Having obtained the desired alcohol LXXXVI we were now ready to attempt the isomerization to lycopodine (I). Treatment of the alcohol LXXXVI with boiling formic acid transformed it to a new

compound which had the same R_f -value as lycopodine (I) on thin layer chromatography. However the infrared spectrum of the product was much different from that of lycopodine (I) and suggested that the O-formate ester LXXXIX of the alcohol had formed since it displayed strong bands at 1730 and 1180 cm^{-1} for the formate ester group as well as a weak band at 1675 cm^{-1} for the olefinic double bond. The N.M.R. spectrum of the compound confirmed that the O-formate ester LXXXIX had formed

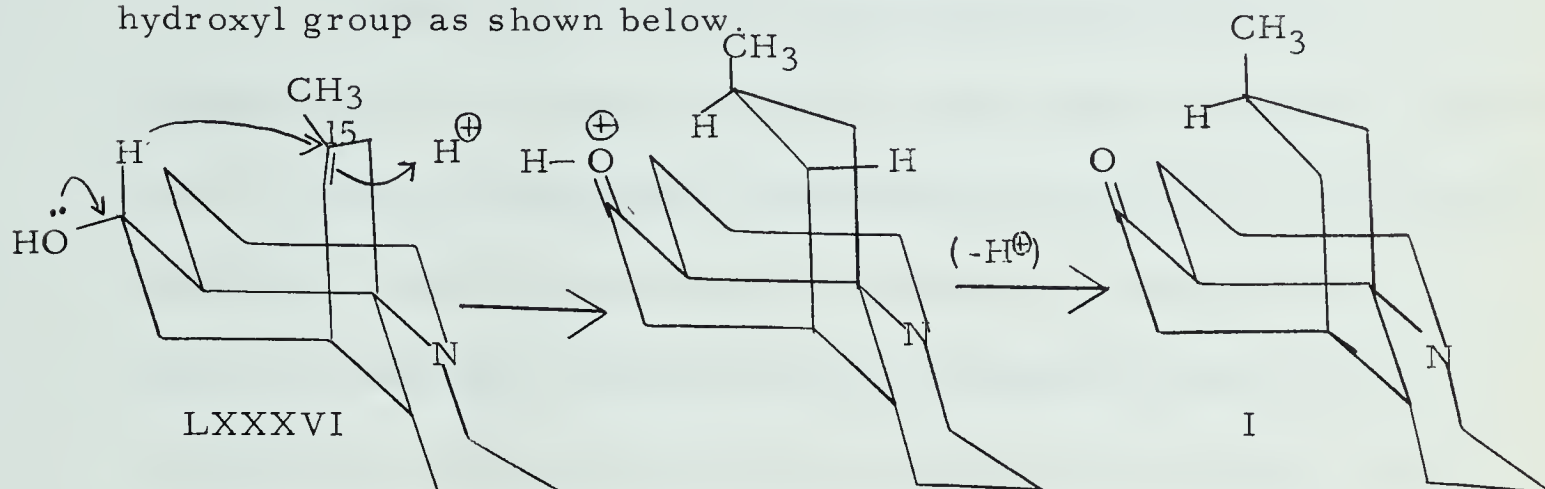


since, in addition to signals at τ 8.32 for the allylic C-15 methyl group and τ 4.50 for the vinylic C-8 proton, it contained a one proton singlet at τ 1.95 for the proton on the formate ester group.

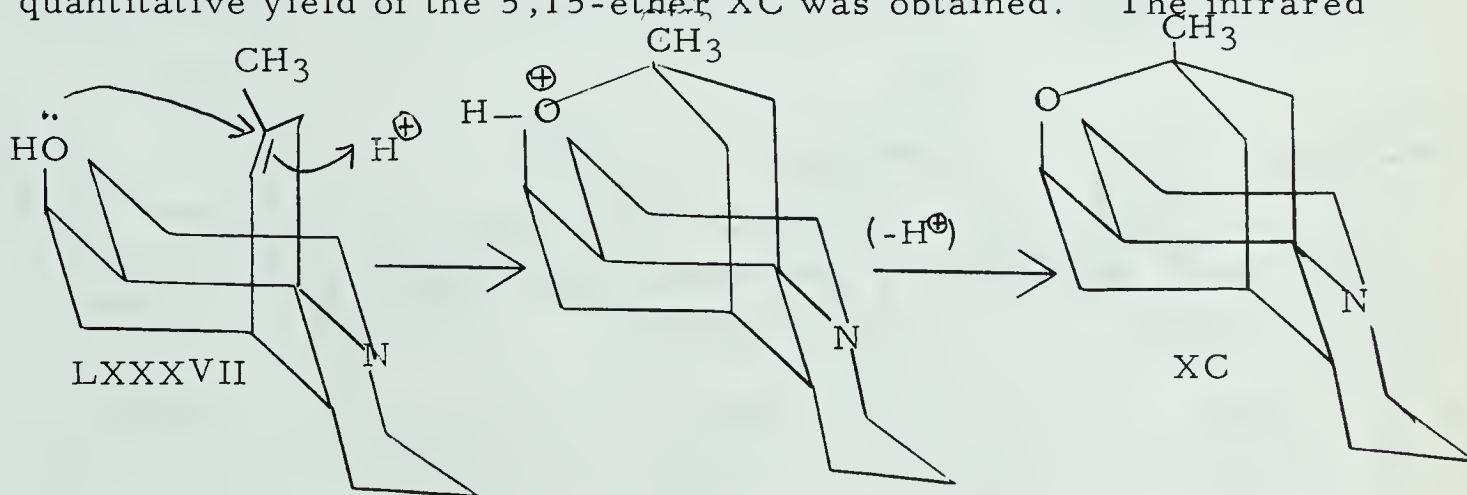
When a solution of the alcohol LXXXVI in 75% aqueous sulfuric acid was stirred at room temperature for twenty-six hours a high yield of a crystalline compound which was identical (infrared spectrum in carbon tetrachloride, thin layer chromatographic behavior) with authentic lycopodine (I), was obtained.

A portion of the synthetic lycopodine was converted to the perchlorate which proved to be identical (infrared spectrum in Nujol, m.p., m.m.p.) with authentic lycopodine perchlorate.

Presumably the transformation of the alcohol LXXXVI into lycopodine (I) involves protonation of the double bond followed by a C-5 to C-15 hydride shift with participation of the equatorial C-5 hydroxyl group as shown below.



When a solution of the unsaturated axial C-5 alcohol LXXXVII in 75% sulfuric acid was stirred at room temperature a quantitative yield of the 5,15-ether XC was obtained. The infrared

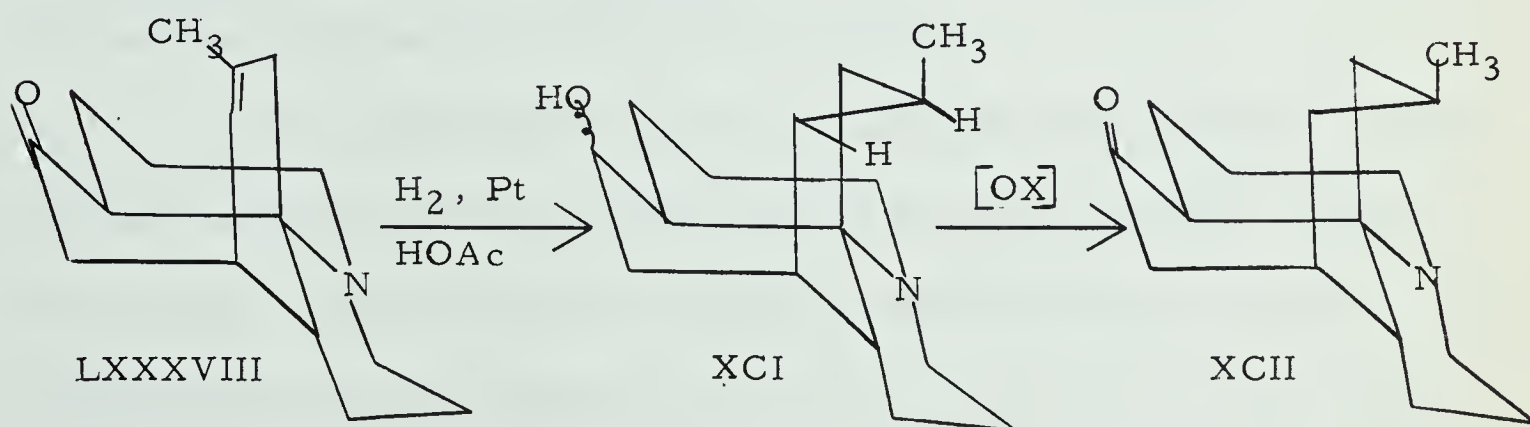


spectrum of the ether XC was void of both hydroxyl and carbonyl absorption. The N.M.R. spectrum was consistent with the structure assigned as it had no olefinic signals but contained a sharp singlet at τ 8.81 for the C-15 methyl group and a one proton signal at τ 6.24 for the equatorial C-5 proton.

The facile formation of the 5,15-ether XC from the axial

C-5 alcohol LXXXVII was expected since protonation of the double bond leads to the formation of a carbonium ion which is readily stabilized by the electron pair on the axial C-5 hydroxyl group.

It was now necessary to show that normal catalytic hydrogenation of the double bond on the bridge ring in the ketone LXXXVIII does not lead to the lycopodine stereochemistry at C-15. 8,15-Dehydrolycopodine LXXXVIII was resistant to catalytic reduction under a variety of conditions, but when it was hydrogenated in acetic acid over platinum oxide at atmospheric pressure a single product, more polar than the starting ketone LXXXVIII, was obtained. That both the double bond and the ketone function had been reduced was apparent from spectral data. The saturated alcohol XCI absorbed in the infrared at

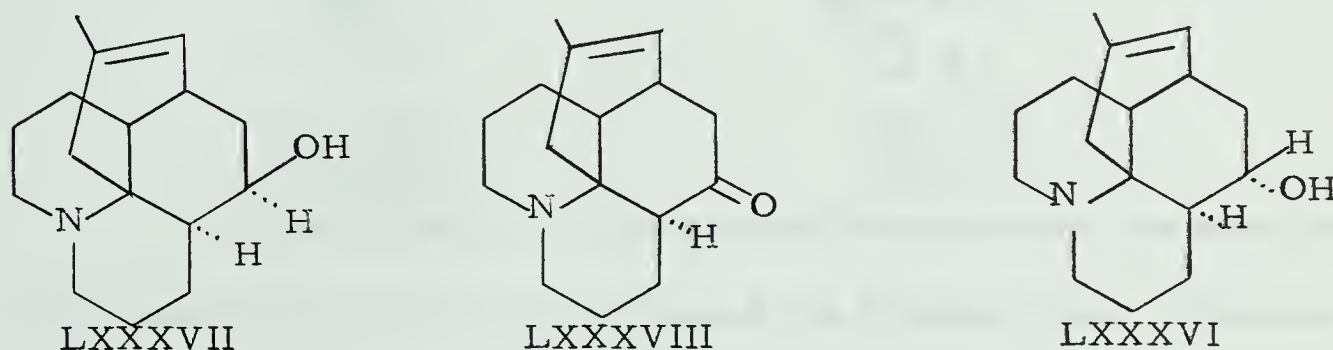


3610 cm^{-1} (in carbon tetrachloride) and no longer contained a carbonyl function. The N.M.R. spectrum no longer contained olefinic signals and the C-15 methyl group now appeared as a doublet ($J=6\text{ cps}$) at $\tau\ 9.12$. The one proton signal at $\tau\ 6.15$ was assigned to the C-5 proton.

Oxidation of the alcohol XCI by the modified Oppenauer procedure (51) afforded deoxyannofoline XCII, m.p. $87-89^{\circ}\text{C}$, the

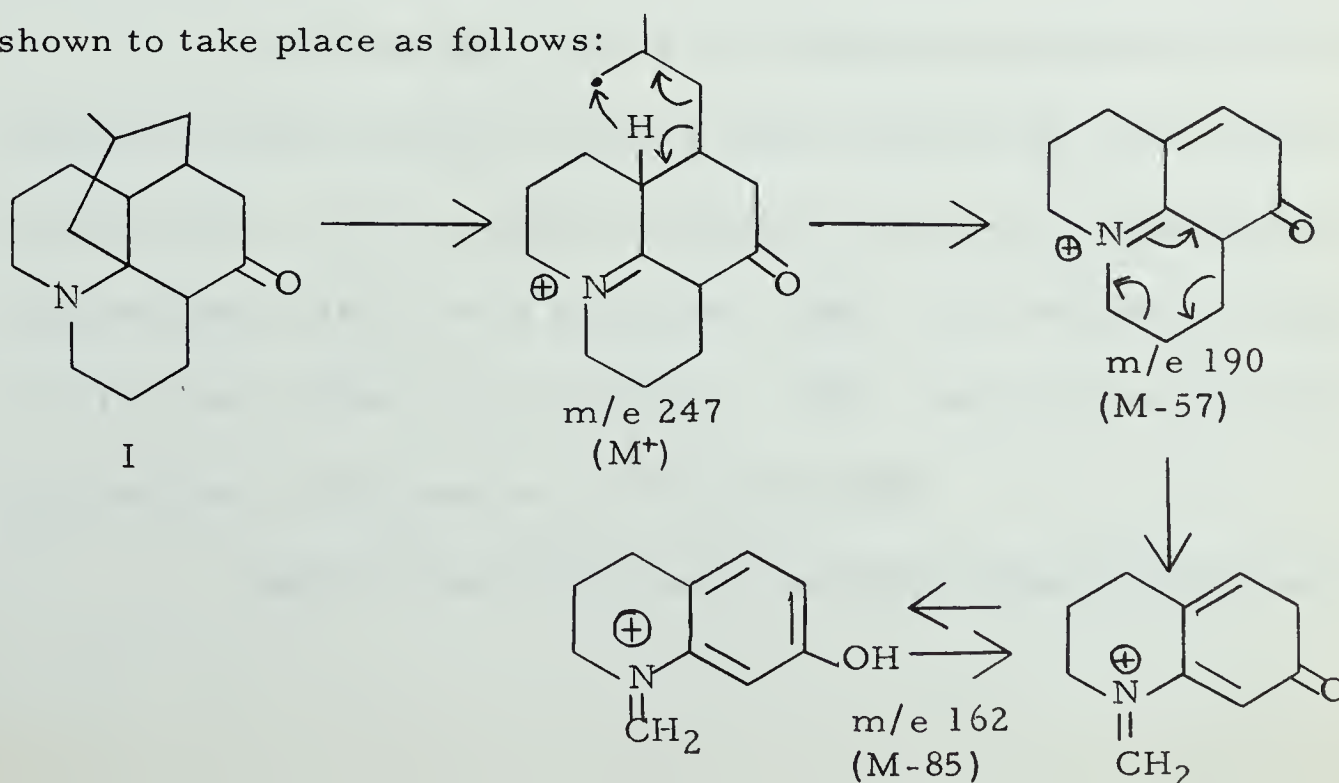
infrared spectrum of which was identical with that of authentic deoxyannofoline. The formation of deoxyannofoline confirms that the hydrogenation of the double bond in the ketone LXXXVIII occurred from the less hindered side of the molecule, as expected, thus giving the opposite stereochemistry at C-15 to that of lycopodine (I).

The mass spectra of the three unsaturated compounds $\Delta^{8(15)}\beta$ -dihydrolycopodine (LXXXVII), 8,15-dehydrolycopodine (LXXXVIII) and $\Delta^{8(15)}\alpha$ -dihydrolycopodine (LXXXVI), obtained in

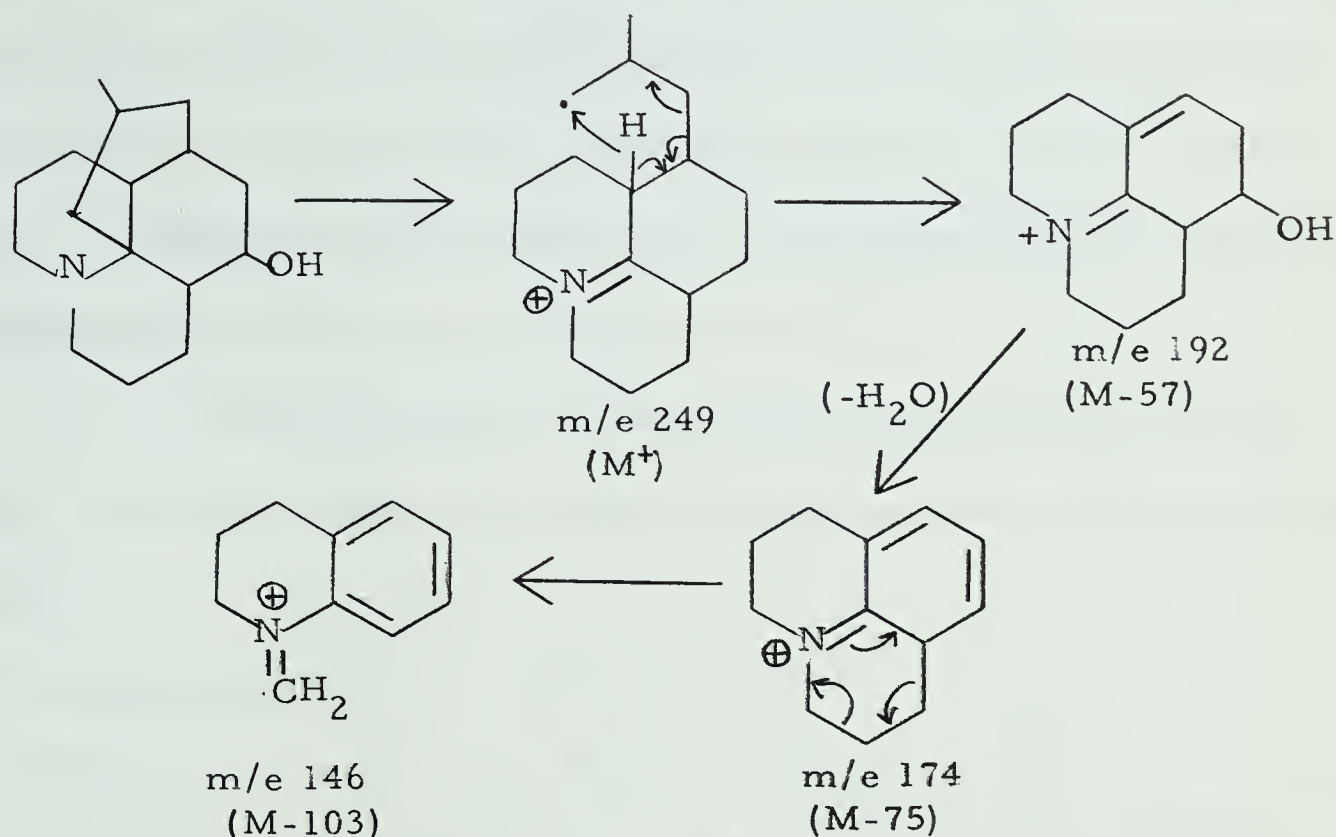


this series contained some interesting features.

The fragmentation pattern of alkaloids containing the normal lycopodine-type skeleton has been discussed by MacLean (52). Thus the principle mode of fragmentation of lycopodine (I) itself has been shown to take place as follows:



Dihydrolycopodine (XV) fragments in a similar fashion.



In the alkaloids of lycopodine-like structure the main mode of fragmentation involves initial loss of the bridging ring. However in the three unsaturated compounds in our series the fragmentation pattern appeared to be much different from that usually observed. Only a small amount of the fragmentation appeared to take place by the schemes outlined above.

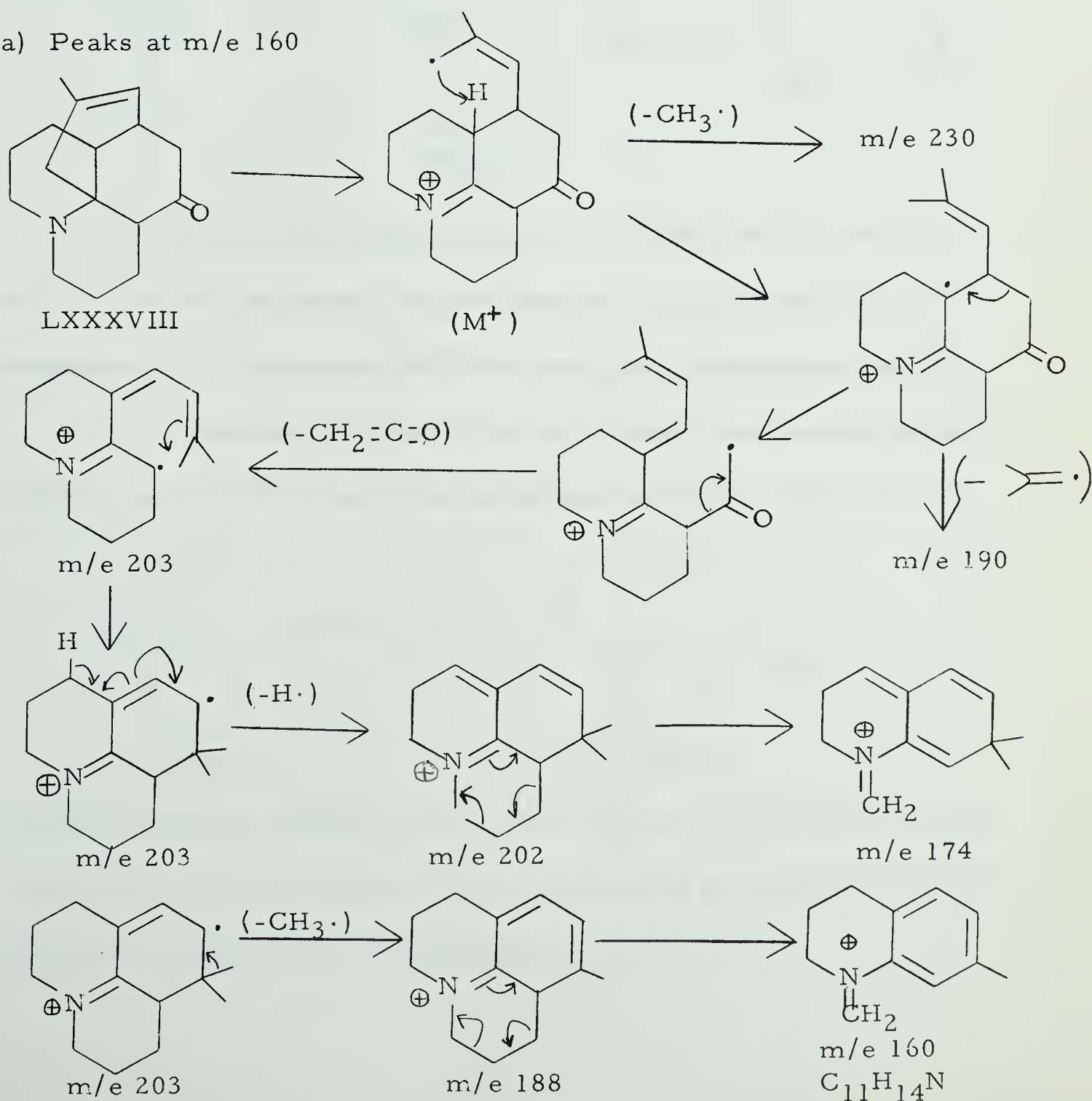
The mass spectrum of 8,15-dehydrolycopodine (LXXXVIII) contained a parent peak at m/e 245 which was also the base peak in the spectrum. Other significant peaks in the spectrum appeared at m/e 230 ($M-15$, 16%), m/e 203 ($M-42$, 16%), m/e 202 ($M-43$, 27%), m/e 190 ($M-55$, 38%), m/e 188 ($M-57$, 21%), m/e 174 ($M-71$, 19%), m/e 160 ($M-85$, 48%) and m/e 137 ($M-108$, 83%).

The only peak in the spectrum of the unsaturated ketone

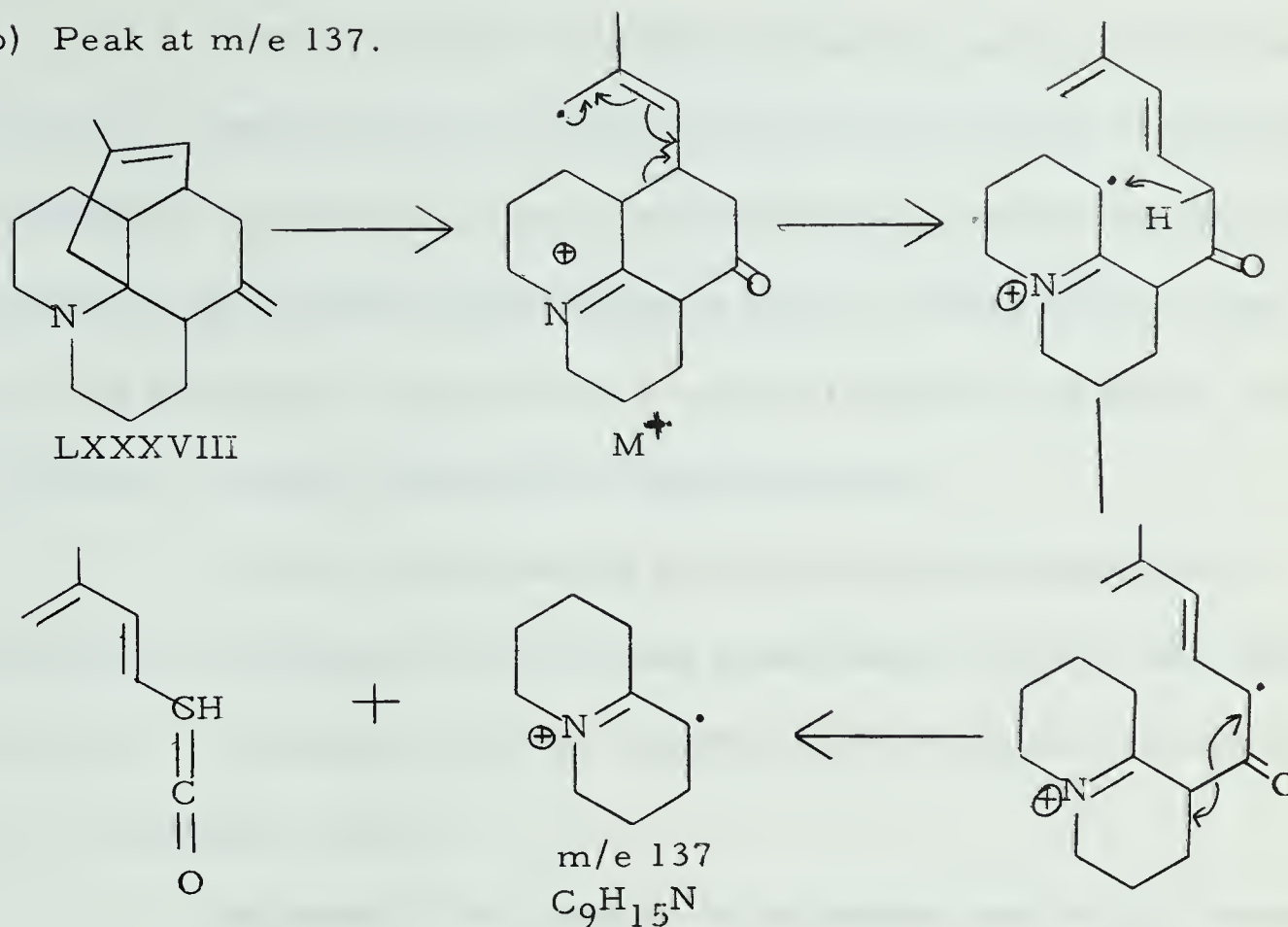
LXXXVIII which can be rationalized on the basis of the usual fragmentation pattern shown above is the peak occurring at m/e 190 since loss of the bridge ring from the molecular ion would result in a fragment of this mass. To explain the mass spectrum of the ketone LXXXVIII different fragmentation schemes must be considered.

A proposal which can rationalize the formation of all the peaks, and which involves two competing fragmentation paths is outlined below.

a) Peaks at m/e 160

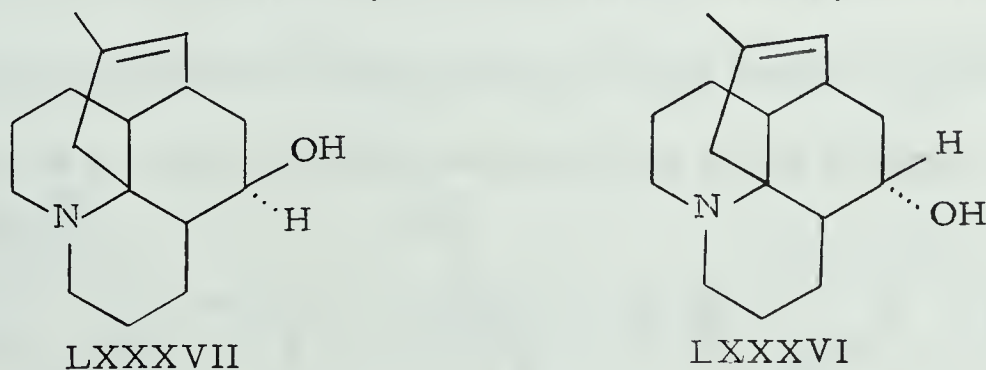


b) Peak at m/e 137.



Exact mass determination of the peaks at m/e 160 and m/e 137 reveal that their compositions are $C_{11}H_{14}N$ and $C_9H_{15}N$ respectively, in agreement with the postulated fragmentation pattern.

The mass spectra of the two epimeric unsaturated alcohols LXXXVI and LXXXVII may also be rationalized by the above scheme.

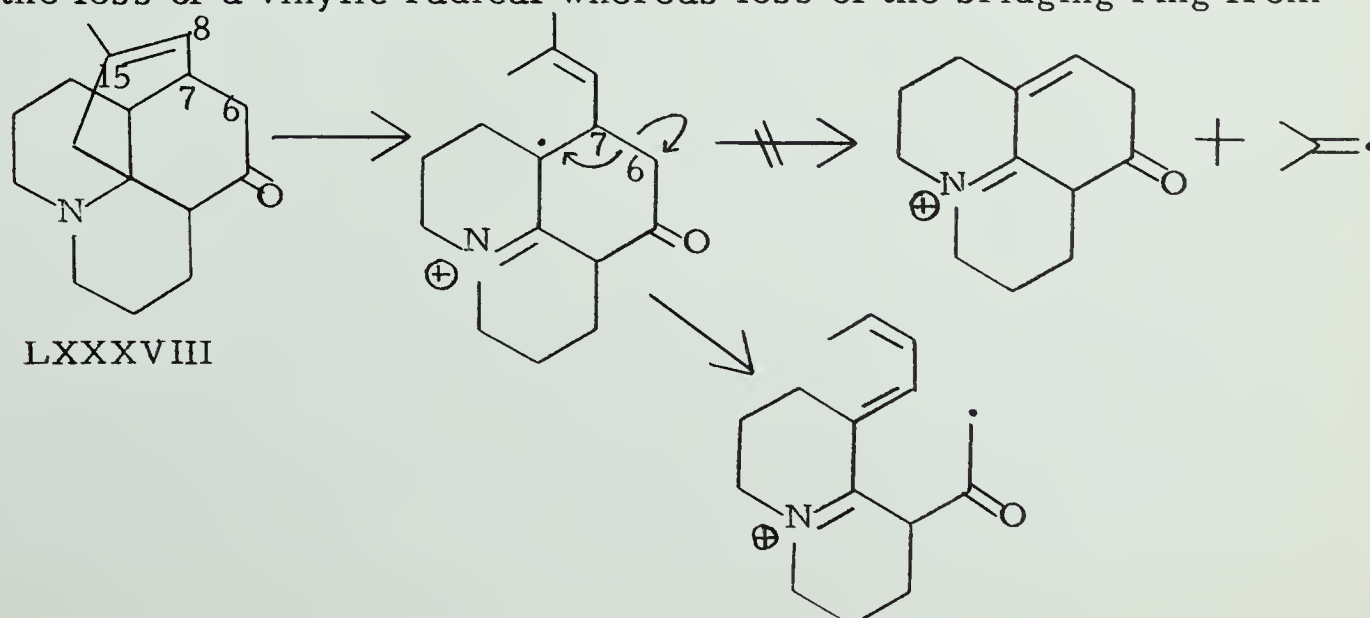


Both alcohols had molecular ions at m/e 247 and both contained peaks at m/e 232, m/e 229, m/e 160 (base peak in the spectrum of LXXXVI) and m/e 137 (base peak in the spectrum of LXXXVII).

The fact that both alcohols contain the peaks m/e 160 and m/e 137, both of which are present in the mass spectrum of the ketone LXXXVIII, confirms that these fragments must be formed by loss of a portion of the molecule which includes the C-5 carbon which in the case of the ketone, is present as a carbonyl function and which, in the alcohols, carries a proton and a hydroxyl group.

It must be pointed out that the proposed fragmentation scheme is not supported by labelling experiments, but it is one which appears to rationalize the mass spectra of the unsaturated compounds in a reasonable manner.

Apparently the presence of the double bond in 8,15 position largely prevents loss of the bridging ring. There are several possible reasons why the bridging ring is not lost readily from the unsaturated compounds. First, the molecular ion (M^+) is an allylic radical, and does not fragment as readily as the less stable alkyl radical in the molecular ion derived from lycopodine (I). Secondly, loss of the bridging ring from the molecular ion of the ketone LXXXVIII involves the loss of a vinylic radical whereas loss of the bridging ring from



lycopodine (I) involves the loss of an alkyl radical. The former process is not as favored energetically as the latter (82). Also, in the molecular ion of the ketone LXXXVIII, the C-6 to C-7 bond is an allylic bond and hence may be more easily cleaved than the C-6 to C-7 bond in lycopodine, thus giving rise to the diene shown above.

The sequence of reactions discussed above provides a method for adding hydrogen to the more hindered side of C-15 thus giving the lycopodine stereochemistry at that center. This transformation is of potential importance in the total synthesis of lycopodine, since now a total synthesis of the unsaturated amido acetate LI, which was prepared via a sequence involving compounds not oxidized in the bridging ring (see section A), would in fact represent a total synthesis of lycopodine (I).

EXPERIMENTAL

Optical rotatory dispersion spectra were measured on a Rudolph Automatic Recording Spectropolarimeter.

Nuclear magnetic resonance spectra were measured in deuterio-chloroform solution, unless otherwise specified, using a Varian Associates Model A-60 spectrometer or a Varian Associates Model HR-100 spectrometer with tetramethylsilane as an internal standard.

Infrared spectra were recorded on a Perkin-Elmer Model 421 dual grating infrared spectrophotometer or a Perkin-Elmer Model 337 grating infrared spectrophotometer.

Mass spectra were recorded on an A.E.I. model MS-2H or an A.E.I. model MS-9 mass spectrometer.

Melting points were determined on a hot-stage Fischer-Johns melting point apparatus and are uncorrected.

Alumina, unless otherwise specified, means basic alumina of activity III-IV (Brockman scale).

Research Specialty Company Aluminum Oxide G was used for thin layer chromatography. R_f value = distance moved by compound / distance moved by solvent.

Microanalyses are by C. Daessle, Montreal, Quebec.

Solutions were dried over anhydrous magnesium sulfate.

OXIDATION OF LYCOPODINE (I)

1. With Potassium Permanganate at Room Temperature

Lycopodine (I) (4.84 g, 19 mmole) was dissolved in 400 ml of acetone (purified by refluxing over excess potassium permanganate and then distillation from anhydrous potassium carbonate). To this solution was added potassium permanganate (6.1 g, 38.5 mmole) in small portions over a period of four and one half hours. During this time the reaction mixture was cooled so that the temperature did not rise above 25°C. When all the permanganate had been used up, the solvents were removed on the evaporator and the residues were dissolved in dilute hydrochloric acid. The pH of the aqueous solution was adjusted to four by careful addition of ammonium hydroxide and then the solution was continuously extracted with ether for forty-eight hours.

The ether extracts were washed with a 5% aqueous solution of sodium bicarbonate then dried and evaporated yielding crude neutral material (2.4 g).

The original aqueous solution was basified ($\text{pH} > 10$) with ammonium hydroxide and continuously extracted with ether for twenty-four hours to recover unreacted lycopodine (I) (2.5 g).

The neutral products were chromatographed on alumina (45 g). Elution with ether gave the pure α -lactam LIII identical with that previously prepared by D. B. MacLean (28).

Recrystallization from ether gave colorless needles,

m.p. 162-163^o C (reported (28) m.p. 159-161^oC).

2. With Iodine

Lycopodine (I) (0.25 g, 1.0 mmole) was dissolved in a mixture of tetrahydrofuran (8 ml) and water (6.4 ml) containing sodium bicarbonate (0.43 g). A solution of iodine (0.524 g, 2.1 mmole) in tetrahydrofuran (8.9 ml) was added slowly at room temperature with stirring under a nitrogen atmosphere. After complete addition, stirring was continued for fifteen minutes, then the reaction mixture was cooled in ice water, methylene chloride was added and the contents were transferred to a separatory funnel. The methylene chloride layer was washed first with a sodium thiosulfate solution (5% in water) and then with a dilute (5%) hydrochloric acid solution.

The methylene chloride layer was dried and evaporated to yield neutral material (45 mg). This material appeared to be over oxygenated and no lycopodine lactam (LIII) was obtained.

Basification of the acidic aqueous extracts with ammonium hydroxide followed by chloroform extraction led to recovery of lycopodine (I) (170 mg) which was purified via its perchlorate salt.

3. With Potassium Permanganate in t-butyl alcohol-water

Lycopodine (I) (0.5 g, 2 mmole) was dissolved in a one to one mixture of t-butyl alcohol and water (30 ml). Calcium sulfate dihydrate (0.35 g, 2 mmole) was added and the stirred mixture was cooled to 0^oC. Solid potassium permanganate (0.64 g, 4 mmole) was

added and the reaction mixture was stirred for five minutes at 0°C and then for five minutes at room temperature. The t-butyl alcohol was removed on the evaporator and the residues were dissolved in dilute hydrochloric acid which was then washed with chloroform. The organic extracts were washed with a five per cent solution of sodium bicarbonate to remove acidic components. The chloroform layer was then dried over anhydrous magnesium sulfate and evaporated to give neutral products (400 mg). No lycopodine- α -lactam (LIII) could be isolated from this material.

THE HYDROXYLACTAM (LIV)

Lycopodine lactam (LIII) (1.038 g, 4 mmole) was dissolved in 99% methanol (50 ml) containing sodium hydroxide (0.45 g). Sodium borohydride (2.25 g) was added and the mixture was refluxed for sixteen hours. Most of the solvent was removed on the evaporator and the residues were dissolved in dilute hydrochloric acid. Chloroform extraction gave the hydroxylactam (LIV) as a nearly colorless semi-solid which was crystallized from acetone to give colorless crystals (0.92 g) m.p. 188-189°C. The infrared spectrum in Nujol revealed hydroxyl absorption at 3400 cm^{-1} (broad) and lactam absorption at 1600 cm^{-1} but no ketonic carbonyl absorption.

THE 5,15-ETHER LII

To a solution of the hydroxylactam LIV (0.82 g, 3.1 mmole) in dry benzene (125 ml) was added lead tetracetate (3.2 g) and the

reaction mixture was refluxed for sixteen hours. Water (80 ml) was then added and the resulting suspension was filtered to remove lead oxide. The aqueous layer was washed twice more with chloroform and the combined organic extracts were dried over anhydrous magnesium sulfate and evaporated leaving an almost colorless product which after crystallization from n-hexane gave the 5,15-ether LII (0.759 g) m.p. 178-180°C. The 5,15-ether LII proved to be identical with the product prepared earlier by D. A. Law (25) in a similar fashion.

REACTION OF THE 5,15-ETHER LII WITH ACETIC ANHYDRIDE - SODIUM ACETATE

The 5,15-ether LII (100 mg, 0.38 mmole) was dissolved in acetic anhydride (10 ml) containing sodium acetate (215 mg, 2.6 mmole) and the reaction mixture was refluxed with exclusion of moisture for fifteen hours. To the cooled reaction mixture was added carefully a 5% sodium bicarbonate solution (20 ml). After the initial reaction had subsided the contents of the flask were poured into aqueous ammonium hydroxide. Chloroform extraction gave a dark brown oily product (90 mg) which crystallized from ether-hexane and which was identical with starting material.

THE UNSATURATED AMIDO ACETATE LI

To a solution of the 5,15-ether LII (329 mg, 1.25 mmole) in anhydrous ether (53 ml) containing acetic anhydride (7.1 ml) was slowly added freshly distilled boron trifluoride-etherate (7.1 ml). The

reaction mixture was stirred at room temperature for fifty hours. Ether (50 ml) was added and the reaction mixture was vigorously shaken for ten minutes with aqueous ammonium hydroxide. The aqueous phase was washed twice with chloroform and the combined organic extracts were evaporated to small volume. More chloroform was added and the solution was washed with dilute hydrochloric acid. The residual chloroform layer was dried over anhydrous magnesium sulfate and evaporated leaving a nearly colorless foamy material (400 mg).

The crude product was chromatographed on alumina (14 g). Elution with benzene-ether (2:1) gave the pure unsaturated amido acetate LI.

The olefinic ester showed absorption in the infrared at 1720 and 1240 cm^{-1} (-OAc) and 1615 cm^{-1} (lactam) in carbon tetrachloride and at 1730 and 1230 cm^{-1} (-OAc) and 1635 cm^{-1} (lactam) in Nujol.

The N.M.R. spectrum showed signals at τ 8.07 ($-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$), τ 5.15 (quartet, $>\text{CH}-\text{OAc}$), τ 8.32 (br. singlet, allylic methyl), τ 4.44 (1H, br. doublet, $J=6$ cps, vinylic proton).

The mass spectrum of the olefin showed a parent peak at m/e 303 and a base peak at m/e 243.

Recrystallization of the unsaturated acetate LI from ether furnished colorless crystals, m.p. 151-152°C. A sample was sublimed

for analysis.

Anal. Calcd. for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.29; N, 4.62.

Found: C, 71.22, 71.42; H, 8.15, 8.52; N, 4.64.

HYDROLYSIS OF UNSATURATED AMIDO ACETATE LI

The unsaturated amido acetate LI (68 mg) was heated on the steam bath for eighteen hours in 20% hydrobromic acid (20 ml). The acidic solution was basified with ammonium hydroxide (pH >10) and the product was extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and evaporated yielding colorless crystalline material (52 mg) which was identical (infrared spectrum, melting point, mixed melting point) with the 5,15-ether LII.

EPOXIDATION OF THE UNSATURATED AMIDO ACETATE LI

m-Chloroperbenzoic acid (0.717 g, 4.16 mmoles) dissolved in chloroform (200 ml) was added dropwise with stirring at 0°C to a solution of the unsaturated amido acetate LI (1.26 g, 4.16 mmoles) in chloroform (180 ml). The reaction mixture was stirred at 0°C for ten hours then at room temperature for an additional ten hours. The chloroform solution was then shaken first with an aqueous solution of sodium bisulfite and then with a 5% sodium bicarbonate solution. The organic phase was dried over anhydrous magnesium sulfate and the solvents were removed at the pump yielding nearly colorless crystalline material (1.3 g). Recrystallization from ether gave the 8,15-epoxide LVIII as colorless crystals m.p. 210-212°C.

The infrared spectrum of the 8,15-epoxide showed bands at 1730, 1225 cm^{-1} (-OAc) and 1635 cm^{-1} (lactam) and 930 cm^{-1} (epoxide) in carbon tetrachloride and at 1730, 1224 cm^{-1} (-OAc) and 1625 cm^{-1} (lactam) and 930 cm^{-1} (epoxide) in Nujol.

The N.M.R. spectrum of the epoxide contained signals at τ 8.63 (3H, singlet, $\text{CH}_3\text{-}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{-C-}$), τ 7.97 (3H, singlet, $\text{CH}_3\text{-COO-}$), τ 7.06 (1H, doublet, $J = 6$ cps, $\text{C-}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{-CH-CH}$) and at τ 5.07 (1H, br. quartet, -CH-OAc).

Though analytical figures for the epoxide LVIII were outside the accepted limits, the mass spectrum of the epoxide showed a parent peak at m/e 319. The starting material LI had a parent peak in the mass spectrum at m/e 303.

REACTION OF THE 8,15-EPOXIDE LVIII WITH BORON TRIFLUORIDE-ETHERATE IN BENZENE

Freshly distilled boron trifluoride-etherate (0.4 ml) was added to a solution of the 8,15-epoxide LVIII (122 mg) in dry benzene (50 ml) and the reaction mixture was stirred at room temperature for ten minutes. The reaction mixture was shaken with 5% sodium bicarbonate solution and the organic phase was separated and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the 8-acetoxy-5,15-ether LXIII as a crystalline solid (116 mg).

The acetoxy ether showed infrared absorption at 1735 and 1220 cm^{-1} (-OAc) and 1630 cm^{-1} (lactam) in carbon tetrachloride and

at 1725 and 1225 cm^{-1} (-OAc) and 1625 cm^{-1} (lactam) in Nujol.

The N.M.R. spectrum had signals at τ 8.85 (3H, singlet, $\text{CH}_3-\overset{\text{O}^-}{\underset{\text{O}}{\text{C}}}-\text{C}$), τ 7.92 (3H, singlet, $\text{CH}_3-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-$), τ 6.42 (1H, br. quartet) and τ 5.3 (1H, br. singlet, $\text{CH}-\text{OAc}$).

The pure acetoxy ether LXIII was obtained as colorless crystals by recrystallization from ether, m.p. 204-205°C. A sample was sublimed for analysis.

Anal. Calcd. for $\text{C}_{18}\text{H}_{25}\text{O}_4\text{N}$: C, 67.68; H, 7.89.

Found: C, 67.61, 67.73; H, 7.39, 7.67.

REACTION OF THE 8,15-EPOXIDE LVIII WITH BORON TRIFLUORIDE-ETHERATE IN DIETHYL ETHER.

To a solution of the 8,15-epoxide LVIII (15 mg) in dry ether (10 ml) was added boron trifluoride-etherate (0.05 ml). The reaction mixture was stirred at room temperature for one hour and then was washed with two portions of a 5% solution of sodium bicarbonate in water. The residual ether layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent gave crystalline material (6 mg) the infrared (carbon tetrachloride) spectrum of which was identical with that of the 8-acetoxy-5,15-ether LXIII obtained before (see above).

REACTION OF THE 8,15-EPOXIDE LVIII WITH BORON TRIFLUORIDE IN BENZENE

Dry boron trifluoride was slowly bubbled through a solution of the 8,15-epoxide LVIII (12 mg) in dry benzene (8 ml) for fifty minutes.

Ether (10 ml) was then added and the reaction mixture was shaken with a 5% aqueous sodium bicarbonate solution. The residual organic phase was dried over anhydrous magnesium sulfate and evaporated at the pump. The residues (7.6 mg) crystallized from ether and proved to be identical (infrared spectrum in carbon tetrachloride) with the 8-acetoxy-5,15-ether LXIII obtained before (see above).

REACTION OF THE 8,15-EPOXIDE LVIII WITH 20% HYDROBROMIC ACID

A solution of the 8,15-epoxide LVIII (50 mg) in 20% hydrobromic acid (5 ml) was heated at steam bath temperature for fifteen hours. The cooled reaction mixture was then basified with cold aqueous ammonium hydroxide ($\text{pH} > 10$). Extraction with chloroform followed by drying over anhydrous magnesium sulfate and evaporation of the solvent gave the 8-hydroxy-5,15-ether LXIV as a crystalline solid (35 mg). Recrystallization from ether containing a few drops of acetone gave the pure product as colorless crystals, m.p. $211-212^{\circ}\text{C}$.

The infrared spectrum showed absorption bands at 3610 cm^{-1} (hydroxyl) and 1605 cm^{-1} (lactam) in chloroform and at 3440 cm^{-1} (hydroxyl) and 1600 cm^{-1} (lactam) in Nujol.

The analytical sample was obtained by sublimation of the recrystallized material.

Anal. Calcd. for $\text{C}_{16}\text{H}_{23}\text{O}_3\text{N}$: C, 69.29; H, 8.37.

Found: C, 69.19, 69.32; H, 7.89, 8.05.

ACETYLATION OF THE 8-HYDROXY-5,15-ETHER LXIV

The 8-hydroxy-5,15-ether LXIV (35 mg) obtained by hydrobromic acid treatment of the 8,15-epoxide LVIII (see above) was dissolved in a mixture of acetic anhydride (4 ml) and pyridine (2 ml) and stirred at room temperature for fourteen hours. A few milliliters of chloroform was added and the solvents were removed at the pump. The residues were taken up in water and the product was extracted with chloroform. Evaporation of the solvent gave an oil (33 mg) which crystallized from ether. The product so obtained was identical (m.p., m.m.p., infrared spectrum in carbon tetrachloride) with the 8-acetoxy-5,15-ether LXIII obtained by treatment of the 8,15-epoxide LVIII with boron trifluoride-etherate.

HYDROLYSIS OF THE 8-ACETOXY-5,15-ETHER LXIII

The 8-acetoxy-5,15-ether LXIII (19 mg), obtained by treatment of 8,15-epoxide LVIII with boron trifluoride-etherate (see above), in 20% hydrobromic acid (10 ml) was heated at steam bath temperature for seventeen hours. The cooled solution was then basified ($\text{pH} > 10$) with cold aqueous ammonium hydroxide and extracted thoroughly with chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate and the solvent was removed at the pump. The residues (17 mg) crystallized from ether and proved to be identical with the 8-hydroxy-5,15-ether LXIV obtained by treatment of the 8,15-epoxide LVIII with 20% hydrobromic acid (see above).

THE 8-KETO-5,15-ETHER LXV

To a solution of the 8-hydroxy-5,15-ether LXIV (133 mg, 0.48 mmole) in 95% acetic acid (35 ml) was added chromium trioxide (61 mg, 0.61 mmole) and the resulting solution was stirred at room temperature for eighteen hours. The reaction mixture was then basified with ice cold ammonium hydroxide. Chloroform extraction gave the crude product (118 mg) which crystallized from ether-acetone mixture to yield the 8-keto-5,15-ether LXV as colorless crystals m.p. 215-216°C.

The infrared spectrum (Nujol) showed bands at 1720 cm^{-1} (ketone) and 1620 cm^{-1} (lactam) with no hydroxyl absorption.

The optical rotatory dispersion curve of the ketone showed a negative Cotton effect.

O.R.D. in methanol (c 0.107):

$[\phi]_{589} -280^\circ$, $[\phi]_{500} -280^\circ$, $[\phi]_{400} -410^\circ$, $[\phi]_{319} -1850^\circ$, $[\phi]_{282} 790^\circ$, $[\phi]_{269} 360^\circ$; $[\phi]_{319} - [\phi]_{282} = -2640^\circ$; $a = -26.4$

A sample was sublimed for analysis.

Anal. Calcd. for $\text{C}_{16}\text{H}_{21}\text{O}_3\text{N}$: C, 69.80; H, 7.69.

Found: C, 69.56, 69.74; H, 7.56, 7.92.

ATTEMPTED REDUCTION OF THE 8-KETO-5,15-ETHER LXV

A. With calcium-ammonia

The 8-keto-5,15-ether LXV (29 mg) was dissolved in dry toluene (8 ml) and this solution was added over a period of five minutes

with vigorous stirring to calcium (0.137 g) in liquid ammonia (40 ml). The reaction mixture was stirred for an additional five minutes and then bromobenzene (3 ml) followed by water (10 ml) was added. The ammonia was allowed to evaporate and the resulting white suspension was evaporated to dryness under reduced pressure. The residues were partitioned between dilute hydrochloric acid and chloroform and the aqueous phase was basified ($\text{pH} > 10$) with ammonium hydroxide. Chloroform extraction gave an intractable foam. The infrared spectrum (chloroform) indicated that no reduction had taken place and the product was not further characterized.

B. With Zinc Dust in Acetic Anhydride

The 8-keto-5,15-ether LXV (250 mg) was dissolved in redistilled acetic anhydride (30 ml) and the solution was heated to boiling. Zinc dust (1 g) was added all at once and the vigorously stirred mixture was refluxed for two hours. The reaction mixture was cooled in ice and the zinc dust was removed by filtration and washed well with ether. The combined filtrates were evaporated to dryness yielding 200 mg of material which crystallized from acetone-ether and which proved to be identical with starting material.

HYDROBORATION OF THE UNSATURATED AMIDO ACETATE LI

A. The 8-hydroxy-5-acetoxy lactam LXXII

Excess diborane, generated by the addition of a solution of sodium borohydride (0.160 g) in dry diglyme to a stirred solution of

boron trifluoride etherate (0.8 g) in dry diglyme, was bubbled through a solution of the unsaturated amido acetate LI (0.175 g) in dry tetrahydrofuran with a slow stream of dry nitrogen. The diborane was generated over a period of thirty minutes and the reaction mixture was stirred for an additional fifteen minutes. The reaction flask was immersed in an ice bath and a few pieces of ice were carefully added followed by an aqueous solution of 3N sodium hydroxide (10 ml). Hydrogen peroxide (30%, 8 ml) was then added dropwise to the stirred reaction mixture over a period of twenty minutes and the reaction mixture was stirred at room temperature for an additional thirty minutes. Extraction with chloroform followed by evaporation of the solvent gave the crude product (150 mg) which showed two spots on thin layer chromatography, one having the same R_f as starting material, the other running slower than starting material. The crude reaction product was chromatographed on alumina (6 g).

Elution with ether gave recovered starting material (55 mg).

Elution with chloroform furnished the pure 8-hydroxy-5-acetoxylactam LXXII (105 mg) which was recrystallized from acetone ether to give colorless crystals, m.p. 246-248°C.

The infrared spectrum (Nujol) of the hydroxy lactam demonstrated bands at 3350 cm^{-1} (broad) (hydroxyl), 1730 cm^{-1} , 1240 cm^{-1} (acetoxyl) and 1610 cm^{-1} (lactam).

The N.M.R. spectrum showed significant signals at τ 8.87

(3H, doublet, $J = 6$ cps, $\text{CH}_3\text{-CH-}$), τ 7.93 (3H, singlet, $\text{CH}_3\text{-COO-}$), τ 6.41 (1H, multiplet, -CHOH), τ 5.04 (1H, multiplet, CH-OAc).

The analytical sample was obtained by sublimation of a small portion of recrystallized material.

Anal. Calcd. for $\text{C}_{16}\text{H}_{27}\text{O}_4\text{N}$: C, 67.26; H, 8.47.

Found: C, 67.06, 67.06; H, 8.20, 8.26.

B. 15-Epilofoline (LXXV)

Excess diborane generated by the addition of a solution of sodium borohydride (0.39 g) in freshly dried diglyme (30 ml) to a solution of boron trifluoride-etherate (3.3 g) in dry diglyme (20 ml) was bubbled through a solution of the unsaturated amido acetate LI (659 mg) in freshly dried tetrahydrofuran over a period of one hour. The reaction mixture was stirred for an additional one and one half hours at room temperature and then was cooled in an ice bath. A few pieces of ice were added (caution) followed by 3N sodium hydroxide (13 ml) and then hydrogen peroxide (10 ml, 30%) dropwise with stirring and cooling. The mixture was stirred for one hour during which it was allowed to warm to room temperature and then the product was extracted with chloroform. Evaporation of the solvent gave a nearly colorless semi-solid (500 mg) which was dissolved in dilute hydrochloric acid.

Chloroform extraction of the acidic solution gave a neutral product (180 mg) which did not appear to contain a lactam group (no absorption between $1600\text{-}1650\text{ cm}^{-1}$ in infrared) but which may have

been an amine-boron complex (absorption bands at 2400, 2340 and 2300 cm^{-1} of medium intensity in chloroform solution). This product was not further characterized.

Basification of the residual acidic aqueous phase followed by chloroform extraction gave the basic product as a colorless oil (200 mg) which crystallized from acetone-ether. Recrystallization from acetone-ether furnished pure 15-epilofoline (LXXV), m.p. 179-180°C.

15-Epilofoline (LXXV) showed infrared bands at 3605 cm^{-1} (hydroxyl) and 1730 cm^{-1} (acetoxyl) in chloroform and at 3420 cm^{-1} (hydroxyl) and 1730 cm^{-1} and 1230 cm^{-1} (acetoxyl) in Nujol.

In the N.M.R. spectrum significant signals appeared at τ 8.9 (3H, doublet, $J = 5.5$ cps, $\text{CH}_3\text{-CH-}$), τ 7.95 (3H, singlet, $\text{CH}_3\text{-COO-}$), τ 6.46 (1H, multiplet, >CH-OH), and τ 5.01 (1H, multiplet, >CH-OAc).

The analytical sample was obtained by sublimation of an extensively recrystallized sample.

Anal. Calcd. for $\text{C}_{18}\text{H}_{29}\text{O}_3\text{N}$: C, 70.32; H, 9.51.

Found: C, 70.35, 70.31; H, 9.52, 9.16.

LITHIUM ALUMINUM HYDRIDE REDUCTION OF THE 8-HYDROXY-5-ACETOXY LACTAM LXXII

To a solution of the hydroxy lactam LXXII (31 mg) in dry ether (30 ml) was added lithium aluminum hydride (91 mg) and the

mixture was heated under reflux for twelve hours. The excess hydride was destroyed by successive addition of water (0.09 ml), 15% sodium hydroxide (0.09 ml), and water (0.27 ml). The salts were then removed by filtration and washed well with chloroform. The combined filtrates were evaporated yielding the product (26 mg) which crystallized from methanol-acetone. Recrystallization furnished the pure 5,8-diol LXXIII, m.p. 260-261°C.

The infrared spectrum in Nujol showed only hydroxyl absorption at 3400 cm^{-1} with no absorption in the carbonyl region.

LITHIUM ALUMINUM HYDRIDE REDUCTION OF ANNOFOLINE (V)

Lithium aluminum hydride (270 mg) was added to a solution of annofoline (V) (93 mg) in dry ether (70 ml) and the reaction mixture was refluxed for sixteen hours. The excess hydride was decomposed by successive addition of water (0.9 ml), 15% sodium hydroxide (0.3 ml) and water (0.9 ml). The salts were removed by filtration through anhydrous sodium sulfate which was then washed well with chloroform. Evaporation of the combined filtrates gave α -dihydroannofoline (LXXIV) (80 mg) which crystallized from acetone-methanol m.p. 265-266°C.

The infrared spectrum (Nujol) of α -dihydroannofoline (LXXIV) showed broad hydroxyl absorption at 3260 cm^{-1} and was not identical with that of the 5,8-diol LXXIII isolated from lithium aluminum hydride reduction of the 8-hydroxy-5-acetoxy lactam LXXII (see above).

However examination of the mother liquors from the crystalline

α -dihydroannofoline (LXXIV) by thin-layer chromatography revealed two spots one having the same R_f as α -dihydroannofoline (LXXIV), the other having the same R_f as the 5,8-diol LXXIII obtained above.

OXIDATION OF 15-EPILOFOLINE (LXXV)

A solution of 15-epilofoline (LXXV) (70 mg) in pyridine (4 ml) was added to a slurry of chromium trioxide (80 mg) in pyridine (0.8 ml) at 0°C. The reaction mixture was stirred at 0°C for one and one half hours and then was allowed to warm to room temperature and stirring was continued for fourteen hours. The reaction mixture was then poured into aqueous ammonium hydroxide and extracted thoroughly with chloroform. Evaporation of the chloroform extracts gave a dark brown oil which was taken up in dilute hydrochloric acid. The acidic solution was washed with two small portions of chloroform to remove non-basic materials and then the aqueous phase was basified with cold aqueous ammonium hydroxide. Chloroform extraction of the basic solution gave a pale yellow oil (60 mg).

Chromatography of the oil through a short column of alumina gave, with benzene-ether eluent, pure O-acetylannofoline (LXXXVII) (55 mg). The synthetic product so obtained was identical (infrared spectrum in carbon tetrachloride, optical rotatory dispersion curve, thin layer chromatographic behavior) with authentic O-acetylannofoline (LXXVII).

Synthetic O-acetylannofoline: ORD in methanol (c 0.150):

$$[\alpha]_{589}^{25} -300^{\circ}, [\alpha]_{305}^{25} -3450^{\circ}, [\alpha]_{275}^{25} 240^{\circ}; [\alpha]_{305}^{25} - [\alpha]_{275}^{25} = -3690^{\circ};$$

$$a_D^{25} -36.9$$

Authentic O-acetyl annofoline: ORD in methanol (c 0.11):

$$[\alpha]_{589}^{25} -300^{\circ}, [\alpha]_{305}^{25} -2640^{\circ}, [\alpha]_{275}^{25} 890^{\circ}; [\alpha]_{305}^{25} - [\alpha]_{275}^{25} = -3530^{\circ};$$

$$a_D^{25} -35.3$$

SYNTHETIC O-ACETYLANNOFOLINE METHIODIDE

Synthetic O-acetylannofoline (LXXVII) (24 mg) was dissolved in one-to-one methanol-acetone (3 ml) and methyl iodide (0.5 ml) was added. The reaction mixture was refluxed for ninety minutes. Ether was then added to the cloud point and the reaction mixture was allowed to cool. The synthetic O-acetylannofoline methiodide so obtained was recrystallized four times, m.p. 288-290°C.

Authentic O-acetylannofoline methiodide had m.p. 289-291°C. The mixed melting point was 288-290°C.

The infrared spectra of synthetic and authentic O-acetylannofoline methiodide in Nujol were superimposable.

SYNTHETIC ANNOFOLINE (V)

To a solution of synthetic O-acetyl annofoline (LXXVII) (50 mg) in methanol (5 ml) was added a 5N sodium hydroxide solution (5 ml) and the reaction mixture was stirred at room temperature for eighteen hours. More water (20 ml) was then added and the aqueous phase was extracted thoroughly with chloroform. Evaporation of the chloroform extracts gave a non-crystalline semi-solid which had the

same R_f on thin layer chromatography as authentic annofoline (V).

The infrared spectrum of the synthetic annofoline (V) in chloroform solution was superimposable on that of an authentic sample of annofoline (V).

ANHYDROLOFOLINE

Lofoline (LXXVI) was dehydrated by the method of Burnell (36). Lofoline (LXXVI) (1.37 g, 4.5 mmole) was dissolved in dry benzene (90 ml) and thionyl chloride (4 ml) was added. The reaction mixture was stirred at room temperature for three and one half hours and then the solvents were removed under reduced pressure. The residues were taken up in water and made basic (pH>10) by addition of ammonium hydroxide. Chloroform extraction yielded a brown oil (1.37 g) which was chromatographed on alumina (25 g). Elution with benzene gave anhydrolofoline (1.13 g) m.p. 102-103°C.

The infrared spectrum showed no hydroxyl absorption and showed acetate absorption at 1730 and 1240 cm^{-1} in carbon tetrachloride and at 1720 and 1250 cm^{-1} in Nujol. Weak double bond absorption occurred at 1675 cm^{-1} in carbon tetrachloride.

The N.M.R. spectrum showed signals at τ 8.35 (3H, br. singlet, $\text{CH}_3\text{-C}\equiv\text{C}$), τ 8.1 (3H, singlet, $\text{CH}_3\text{-COO-}$), τ 5.16 (1H, br. quartet, >CH-OAc) and τ 4.50 (1H, br. doublet, $J=6$ cps, $\text{H-C}\equiv\text{C}$).

The mass spectrum showed a parent peak at m/e 289 with the base peak at m/e 229.

$\Delta^{8(15)}$ -DIHYDROLYCOPODINE (LXXXVII)

A. From anhydrolofoline

A solution of anhydrolofoline (850 mg) in 95% ethanol (20 ml) and 10% aqueous potassium hydroxide (25 ml) was refluxed for nine hours. The reaction mixture was then poured into more water and extracted thoroughly with chloroform. Evaporation of the chloroform extracts gave a nearly colorless solid. Recrystallization from acetone furnished pure $\Delta^{8(15)}$ - β -dihydrolycopodine (LXXXVII) needles, m.p. 93-94°C.

The infrared spectrum showed absorption at 3542 cm^{-1} (concentration independent) and at 1665 cm^{-1} (weak) in carbon tetrachloride and at 3560 and 3200 cm^{-1} (broad) in Nujol.

The N.M.R. spectrum revealed signals at τ 8.30 (3H, br. singlet, $\text{CH}_3\text{-C}\equiv\text{C-}$) and at τ 4.14 (1H, br. doublet, $J=6$ cps, $\text{HC}\equiv\text{C-CH}_3$).

The mass spectrum had a parent peak at m/e 247 with the base peak at m/e 137.

B. From the Unsaturated Amido Acetate LI

To a solution of the unsaturated amido acetate LI (140 mg, 0.46 mmole) in dry ether (40 ml) was added lithium aluminum hydride (0.25 g) and the reaction mixture was refluxed for six hours. Water (0.2 ml), 15% sodium hydroxide (0.2 ml) and water (0.9 ml) were successively added and the reaction mixture was poured into cold aqueous ammonium hydroxide. Chloroform extraction furnished a

colorless solid which was identical (m.p. , m.m.p. , infrared spectrum in carbon tetrachloride) with $\Delta^{8(15)}\text{-}\beta$ -dihydrolycopodine (LXXXVII) obtained by hydrolysis of anhydrolofoline (see above).

8,15-DEHYDROLYCOPODINE (LXXXVIII)

$\Delta^{8(15)}\text{-}\beta$ -Dihydrolycopodine (LXXXVII) was oxidized using the modified Oppenauer oxidation procedure described by Warnhoff (51).

To a solution of $\Delta^{8(15)}\text{-}\beta$ -dihydrolycopodine (LXXXVII) (500 mg , 2.02 mmole) and commercial grade potassium t-butoxide (570 mg , 5.06 mmole) in dry benzene (40 ml) was added fluorenone (1.84 g , 10.15 mmole). The reaction mixture was stirred at room temperature under an atmosphere of nitrogen for two hours. Water (25 ml) and ether (30 ml) were then added and the aqueous phase was washed with two portions of ether. The combined organic extracts were washed with four portions (50 ml each) of 5% hydrochloric acid. The acidic solution was immediately basified by pouring into ice cold ammonium hydroxide. Chloroform extraction of the basic aqueous phase yielded a colorless oil (460 mg) which crystallized from ether. Recrystallization gave 8,15-dehydrolycopodine (LXXXVIII) as colorless crystals , m.p. 126-127.5°C.

The infrared spectrum showed absorption at 1705 cm^{-1} and 1670 cm^{-1} (weak) in carbon tetrachloride and at 1708 cm^{-1} in Nujol.

The N.M.R. spectrum showed signals at τ 8.40 (3H, br. singlet $\text{CH}_3\text{-C=C}$) and at τ 4.58 (1H br. doublet, $J=6\text{ cps}$, HC=C).

The mass spectrum had a parent peak at m/e 245 and other major peaks at m/e 160 and m/e 137.

An extensively recrystallized sample was sublimed for analysis.

Anal. Calcd. for $C_{16}H_{23}ON$: C, 78.32; H, 9.45; N, 5.71.

Found: C, 78.23, 78.43; H, 9.60, 9.69; N, 5.28.

$\Delta^{8(15)}$ - α -DIHYDROLYCOPODINE (LXXXVI)

A solution of 8,15-dehydrolycopodine (LXXXVIII) (442 mg, 1.8 mmole) in methanol (30 ml) was added with vigorous stirring to a cooled flask containing liquid ammonia (200 ml). Lithium metal (0.55 g, 0.09 g. atom) was added to this solution in small pieces over a period of thirty minutes. The ammonia was then allowed to evaporate and the residues were taken up in water (150 ml). Extraction of the aqueous phase with chloroform gave $\Delta^{8(15)}$ - α -dihydrolycopodine (LXXXVI) as a nearly colorless amorphous solid (425 mg) which could not be induced to crystallize.

The infrared spectrum in carbon tetrachloride contained bands at 3610 cm^{-1} and 1675 cm^{-1} (weak) and no carbonyl absorption.

The N.M.R. spectrum had a signal at τ 8.35 (3H, br. singlet, $\text{CH}_3\text{-C=C}$) and τ 4.50 (1H, br. doublet, $J=6$ cps, H-C=C-).

The mass spectrum displayed a parent peak at m/e 247 and the base peak in the spectrum appeared at m/e 160.

The methiodide of $\Delta^{8(15)}$ - α -dihydrolycopodine (LXXXVI) was

prepared in refluxing methanol containing excess methyl iodide.

Recrystallization from acetone-methanol with ether being added to the cloud point gave pure $\Delta^{8(15)}$ - α -dihydrolycopodine methiodide m.p. 288-289°C.

TREATMENT OF $\Delta^{8(15)}$ - α -DIHYDROLYCOPODINE (LXXXVI) WITH FORMIC ACID

A solution of $\Delta^{8(15)}$ - α -dihydrolycopodine (LXXXVI) (57 mg) in formic acid (10 ml) was heated under reflux. After one hour an aliquot was removed and worked up. Thin layer chromatography indicated that no starting material remained but there was a spot running with the same R_f as lycopodine (I). The reaction mixture was then worked up by pouring it into aqueous 10% sodium carbonate solution. Chloroform extraction gave a product which had the same R_f as lycopodine on thin layer chromatography but the infrared spectrum was much different from that of lycopodine (I).

Spectral evidence indicated that the O-formate ester LXXXIX of $\Delta^{8(15)}$ - α -dihydrolycopodine (LXXXVI) had formed.

The infrared spectrum in carbon tetrachloride displayed strong bands at 1730 and 1180 cm^{-1} (formate) as well as weak absorption at 1675 cm^{-1} (double bond).

The N.M.R. spectrum showed bands at τ 8.32 (olefinic methyl group), τ 4.50 (olefinic proton) and a low field signal at τ 1.95 (proton of formyl group).

This product was not further characterized.

SYNTHETIC LYCOPODINE

A solution of $\Delta^{8(15)}-\alpha$ -dihydrolycopodine (LXXXVI) (65 mg) in 75% aqueous sulfuric acid was stirred at room temperature for twenty-six hours. An aliquot was withdrawn and worked up. Thin layer chromatography indicated that a single component was present having an R_f identical with that of lycopodine (I).

The reaction mixture was then worked up by pouring it onto ice and then pouring the cold aqueous solution into ice cold aqueous ammonium hydroxide. Chloroform extraction gave synthetic lycopodine (I) (55 mg) as colorless crystals.

The infrared spectrum in carbon tetrachloride of the synthetic lycopodine so obtained was superimposable on that of authentic lycopodine.

The synthetic product was converted to its perchlorate by heating in acetone containing perchloric acid for a few minutes. The crystalline salt so obtained was recrystallized from acetone, m.p. 275-278°C (d) (undepressed on admixture with authentic lycopodine perchlorate).

The Nujol infrared spectrum of the synthetic lycopodine perchlorate was identical with that of authentic lycopodine perchlorate.

TREATMENT OF $\Delta^{8(15)}-\beta$ -DIHYDROLYCOPODINE (LXXXVII) WITH 75% SULFURIC ACID

$\Delta^{8(15)}-\beta$ -Dihydrolycopodine (LXXXVII) (27 mg) was dissolved

in 75% aqueous sulfuric acid (10 ml) and stirred at room temperature for one hour and fifteen minutes. The reaction mixture was poured onto ice and then poured into ice cold aqueous ammonium hydroxide. Chloroform extraction gave lycopodine-5,15-ether (XC) as a pale yellow oil (26 mg).

The infrared spectrum in carbon tetrachloride contained no hydroxyl or carbonyl absorption.

The N.M.R. spectrum showed a sharp signal at τ 8.81 (3H, singlet, $\text{CH}_3-\overset{\text{O}-}{\underset{|}{\text{C}}}-\text{C}$) and a broad signal at τ 6.24 (1H, br. singlet, $\text{H}-\overset{\text{O}-}{\underset{|}{\text{C}}}-\text{C}$) and contained no olefinic signals.

ATTEMPTED HYDROGENATION OF 8,15-DEHYDROLYCOPODINE (LXXXVIII)

A. Over Palladium-charcoal at atmospheric pressure

8,15-Dehydrolycopodine (LXXXVIII) (54 mg) was dissolved in methanol (20 ml) containing palladium-charcoal (40 mg) and the reaction mixture was stirred under one atmosphere of hydrogen for sixteen hours. Removal of the catalyst by filtration and evaporation of the solvent gave starting material (thin-layer chromatographic behavior and infrared spectrum).

B. Over palladium-charcoal at Fifty P.s.i.

8,15-Dehydrolycopodine (LXXXVIII) (50 mg) was dissolved in methanol (10 ml) containing palladium-charcoal (30 mg) and the reaction mixture was shaken under fifty p.s.i. of hydrogen for twenty-four

hours. Removal of the catalyst and evaporation of the solvent gave only starting material (thin-layer chromatographic behavior and infrared spectrum).

C. Over platinum oxide at atmospheric pressure in methanol

A solution of 8,15-dehydrolycopodine (LXXXVIII) (50 mg) in methanol (10 ml) containing platinum oxide (30 mg) was stirred under one atmosphere of hydrogen for twenty hours. The catalyst was removed by filtration and the solvents evaporated giving a material which was mainly starting material (thin-layer chromatographic behavior and infrared spectrum).

D. Over platinum oxide at atmospheric pressure in acetic acid

A solution of 8,15-dehydrolycopodine (LXXXVIII) (100 mg, 0.41 mmole) in acetic acid (5 ml) containing platinum oxide (50 mg) was stirred under one atmosphere of hydrogen for twenty three hours. The observed hydrogen uptake was 28.7 cc. The catalyst was removed by filtration and washed with chloroform and the combined filtrates were poured into aqueous ammonium hydroxide. Chloroform extraction gave a colorless solid which on thin-layer chromatography showed one major spot running slower than starting material.

Recrystallization from acetone gave pure saturated alcohol XCI, m.p. 191-193°C. Lit. (10) m.p. of dihydrodeoxyannofoline 189-190°C.

The infrared spectrum in carbon tetrachloride showed only

hydroxyl absorption at 3610 cm^{-1} .

The N.M.R. spectrum showed no low field olefinic signals and contained a sharp doublet at τ 9.12 (3H, doublet, $J \approx 6$ cps, $\text{CH}_3\text{-CH}$) and a multiplet at τ 6.15 (1H, multiplet, CH-OH).

DEOXYANNOFOLINE (XCII)

The saturated alcohol XCI obtained in (D) above (60 mg, 0.24 mmole) was dissolved in dry benzene (10 ml) containing commercial grade potassium-*t*-butoxide (66 mg, 0.45 mmole). Fluorenone (216 mg, 1.2 mmole) was added and the reaction mixture was stirred at room temperature for 90 minutes. Water (25 ml) and ether (20 ml) were added and the aqueous phase was washed with two more portions of ether. The combined organic extracts were extracted with four portions of dilute hydrochloric acid. The acidic extracts were basified with cold aqueous ammonium hydroxide. Chloroform extraction of the basic solution gave an oily product which did not crystallize.

Chromatography on alumina (1 g) with benzene as eluent gave crystalline deoxyannofoline (27 mg), m.p. $87\text{-}89^\circ\text{C}$. Lit. (10) m.p. $88\text{-}92^\circ\text{C}$. An infrared spectrum (Nujol mull) of the deoxyannofoline so obtained was identical with an infrared spectrum of authentic deoxyannofoline supplied by F.A.L. Anet.

OPTICAL ROTATORY DISPERSION CURVES.

OPTICAL ROTATORY DISPERSION CURVE
of the 8-KETO-5,15-ETHER LXV
in METHANOL

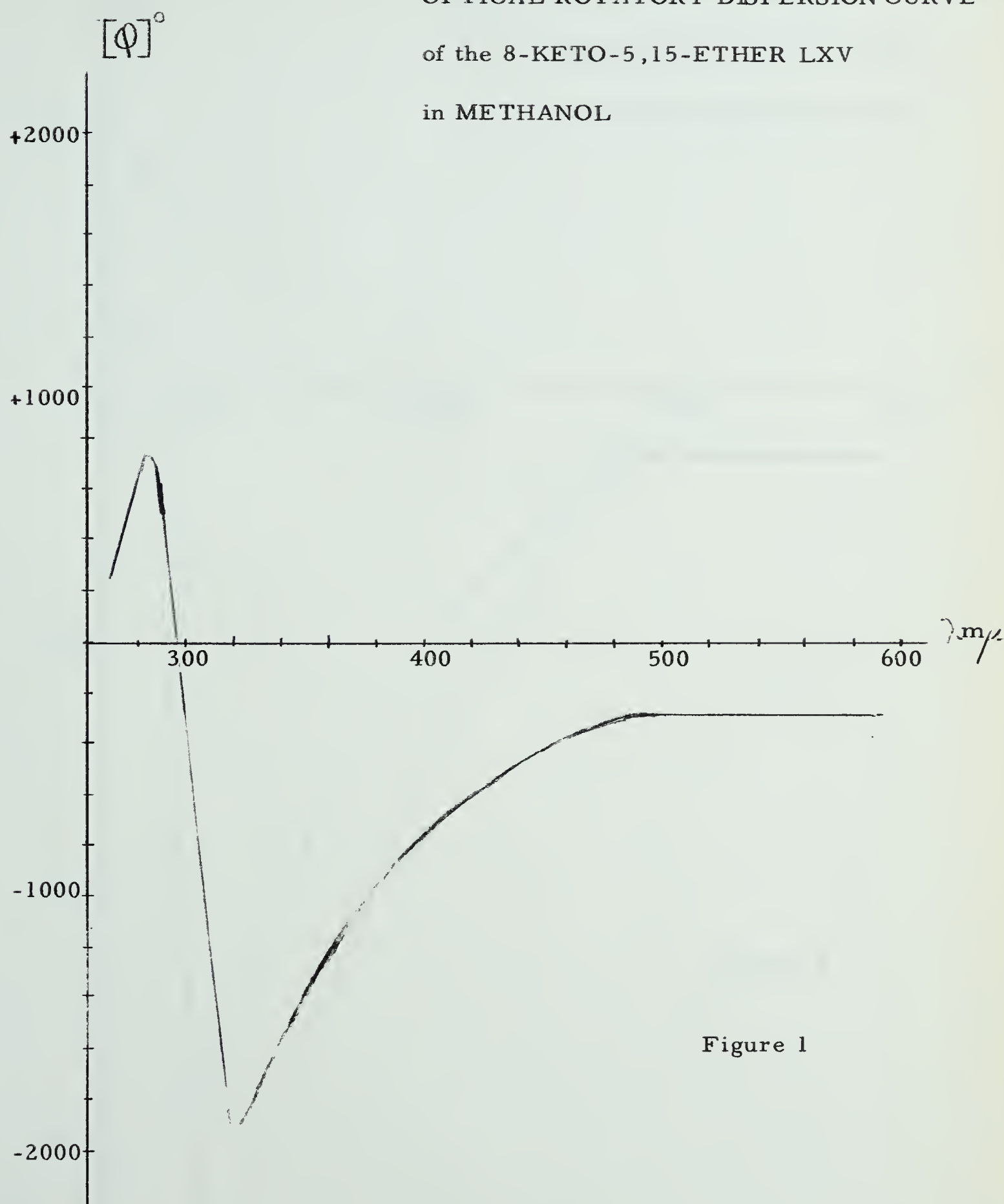


Figure 1

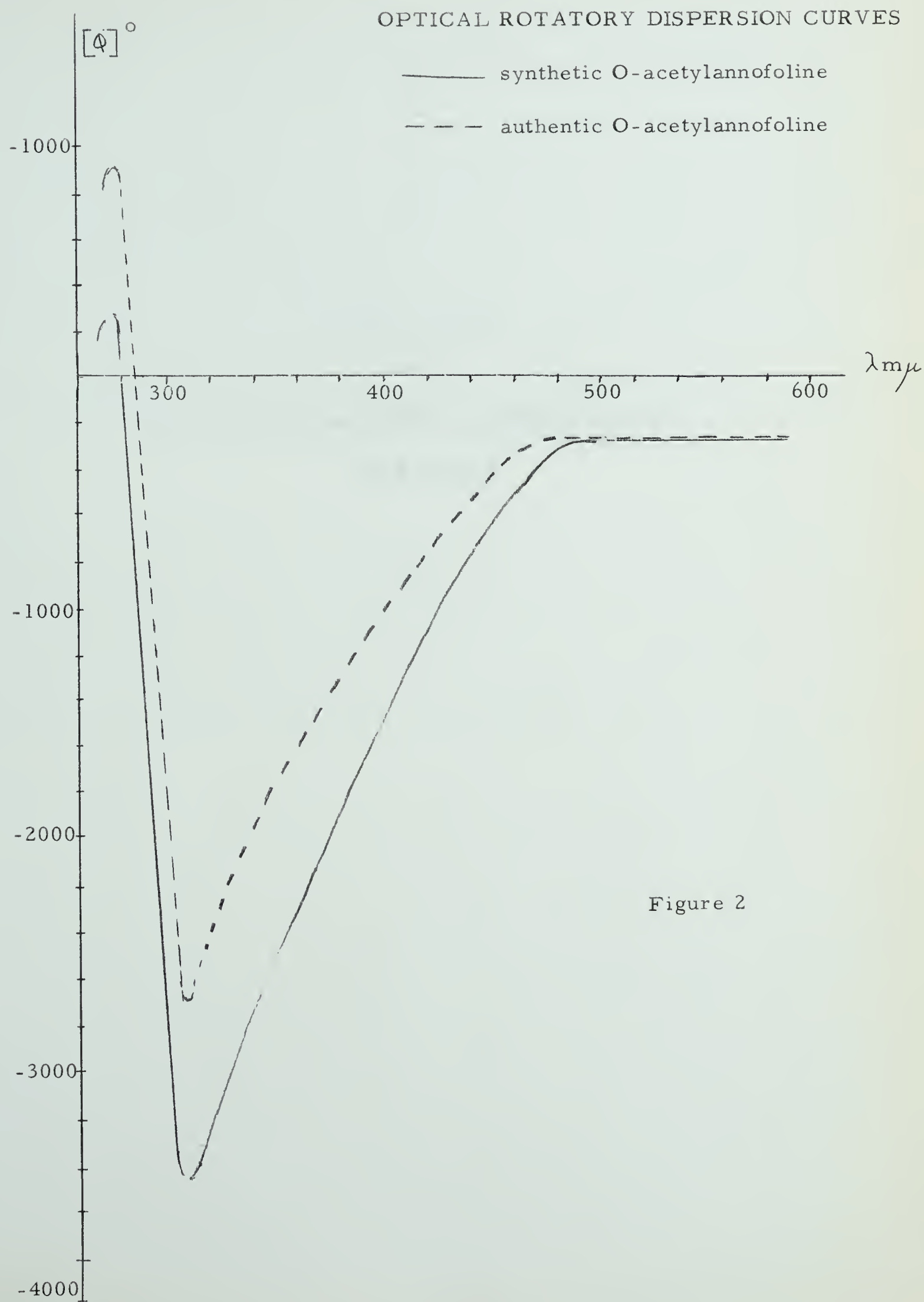


Figure 2

INFRARED
and
NUCLEAR MAGNETIC RESONANCE
SPECTRA

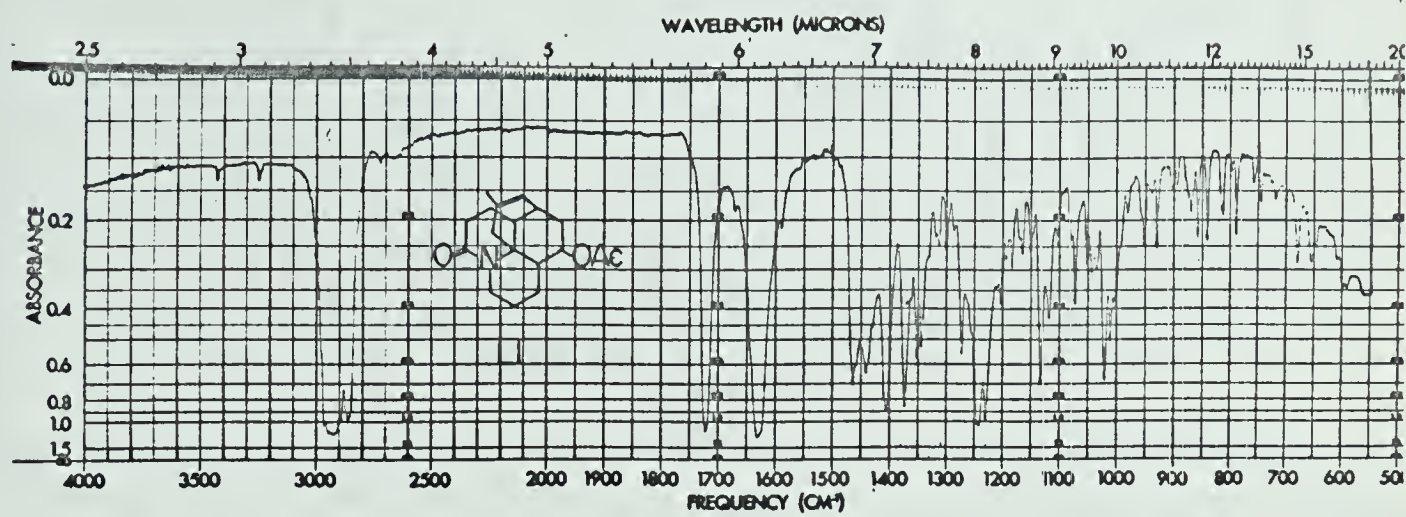


Figure 3

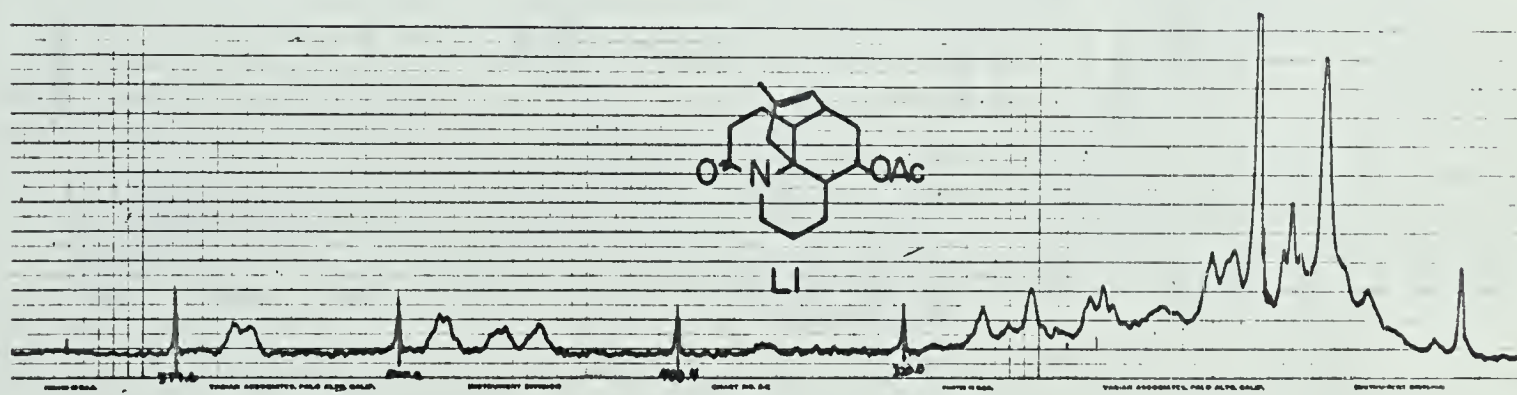


Figure 4

Figure 6

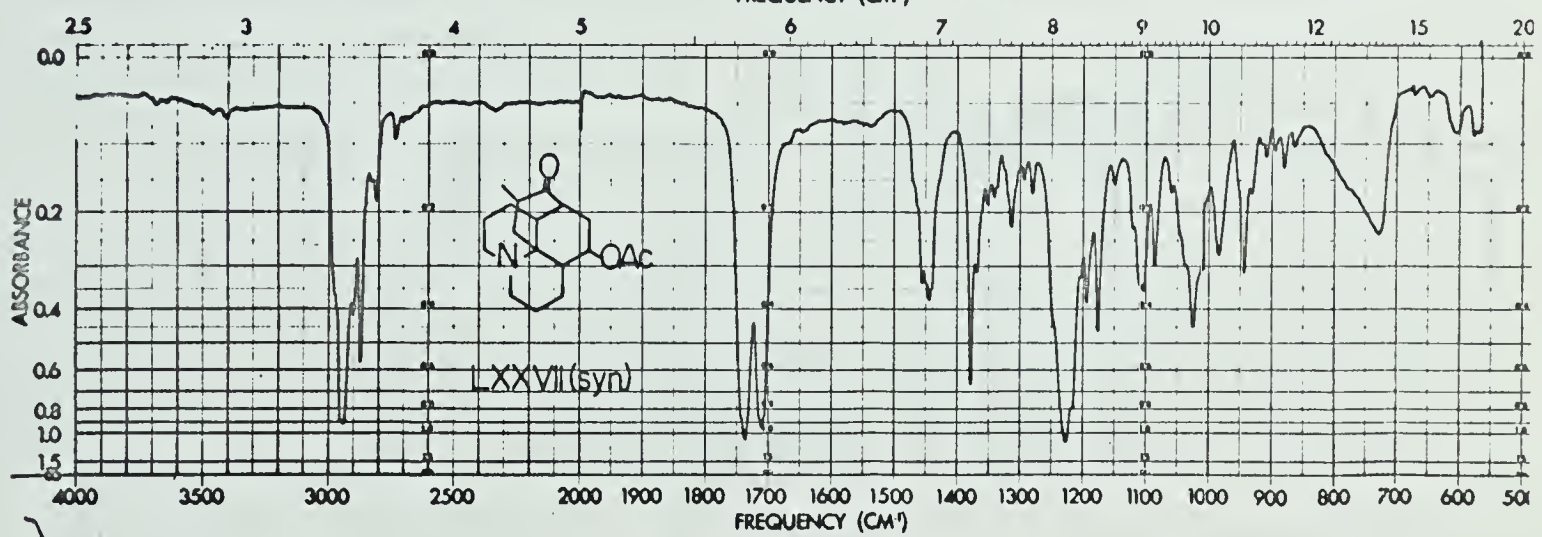
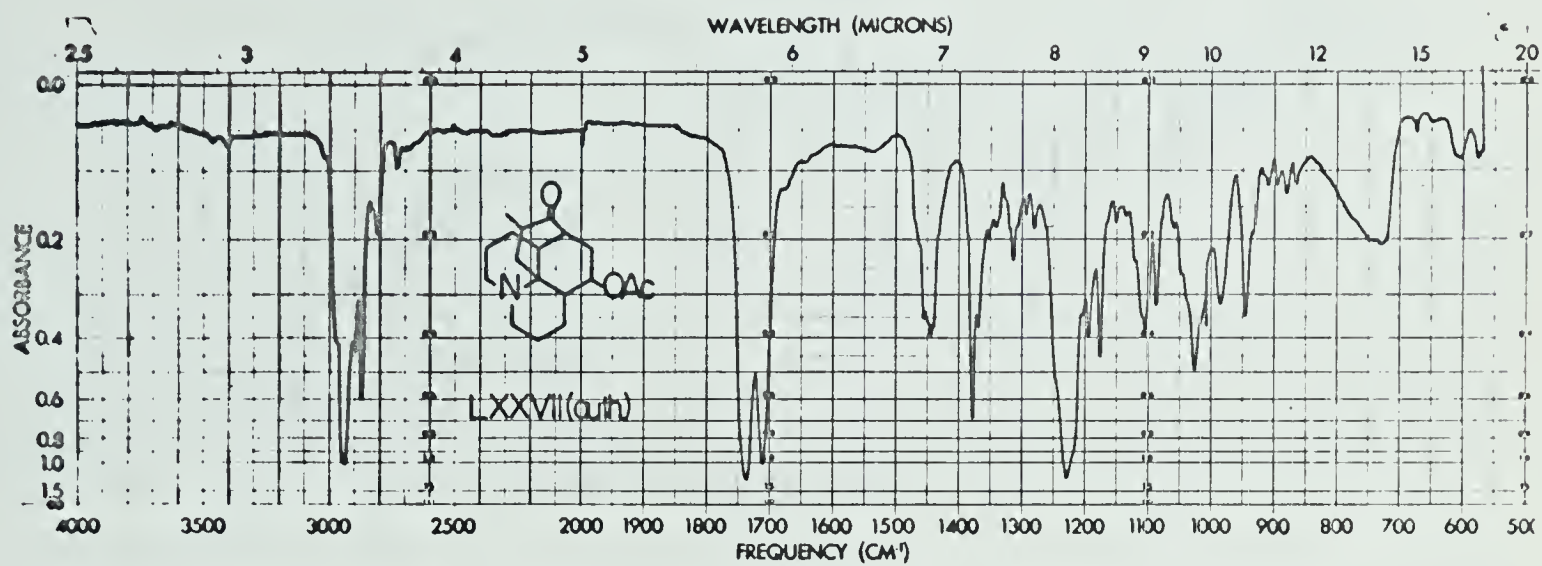


Figure 5

Figure 7

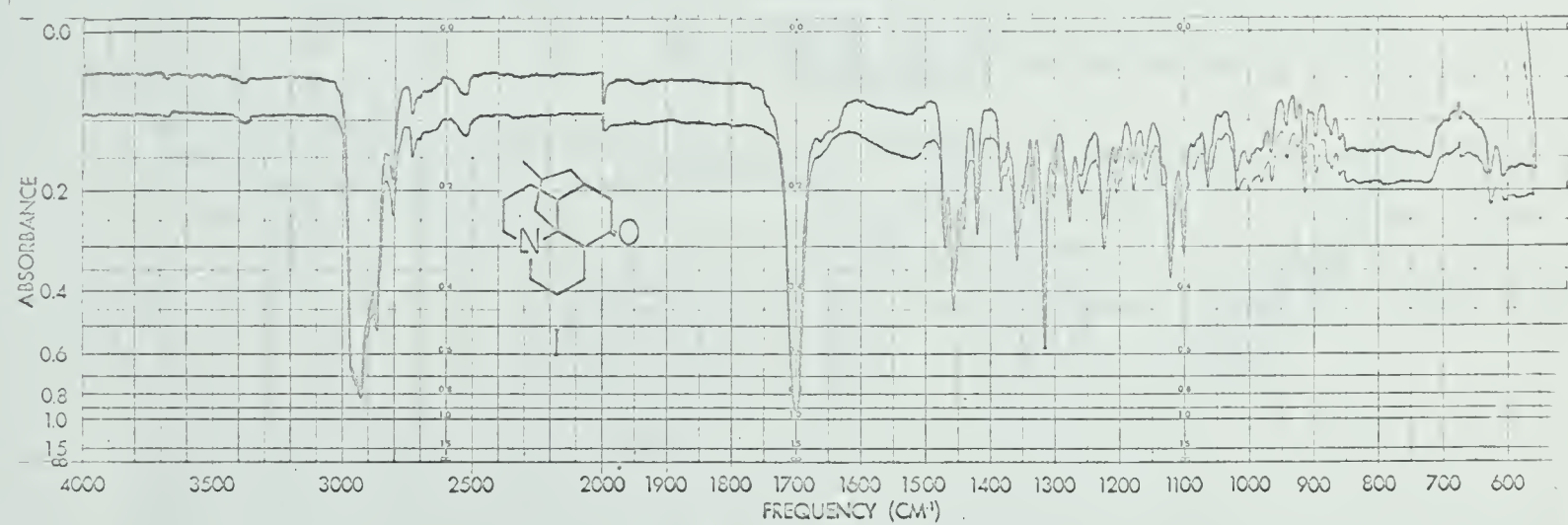
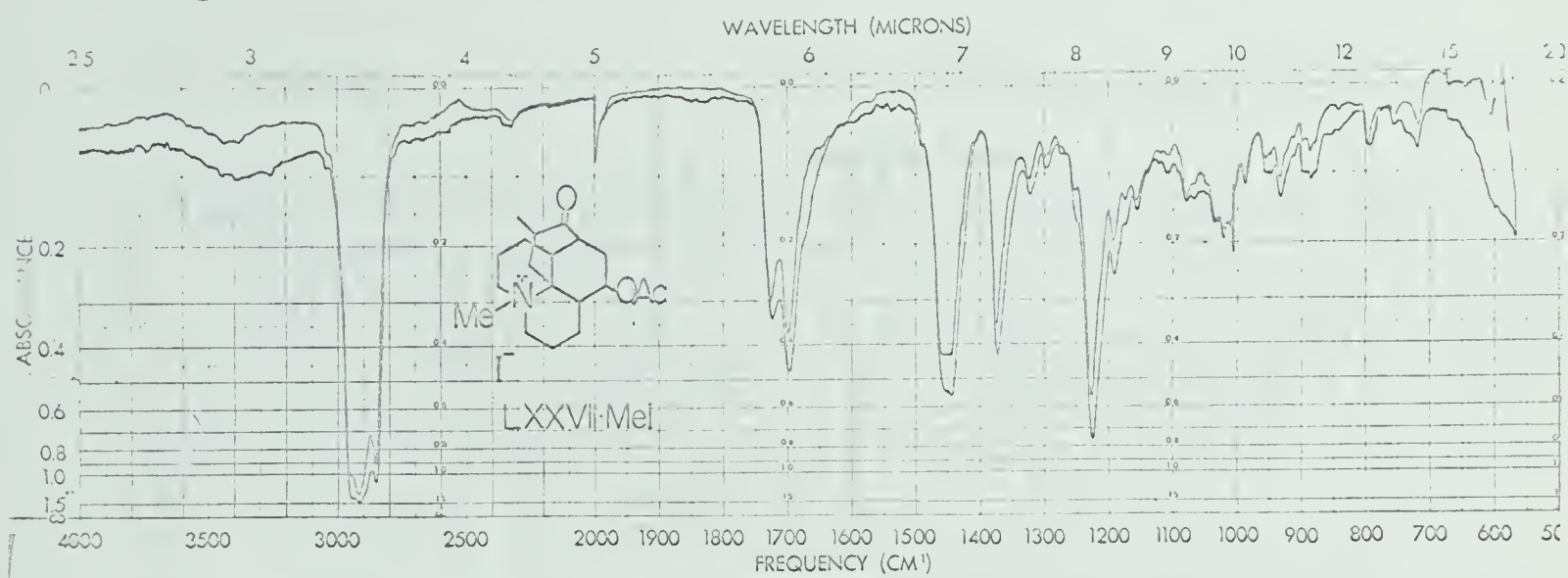


Figure 8

Figure 9

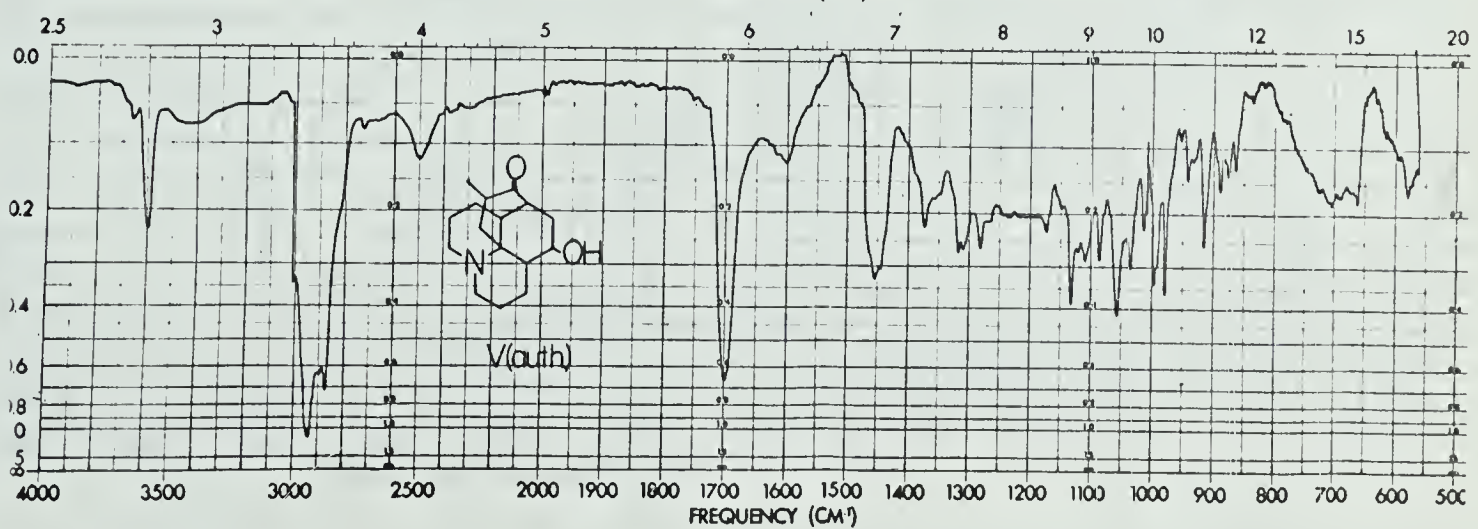
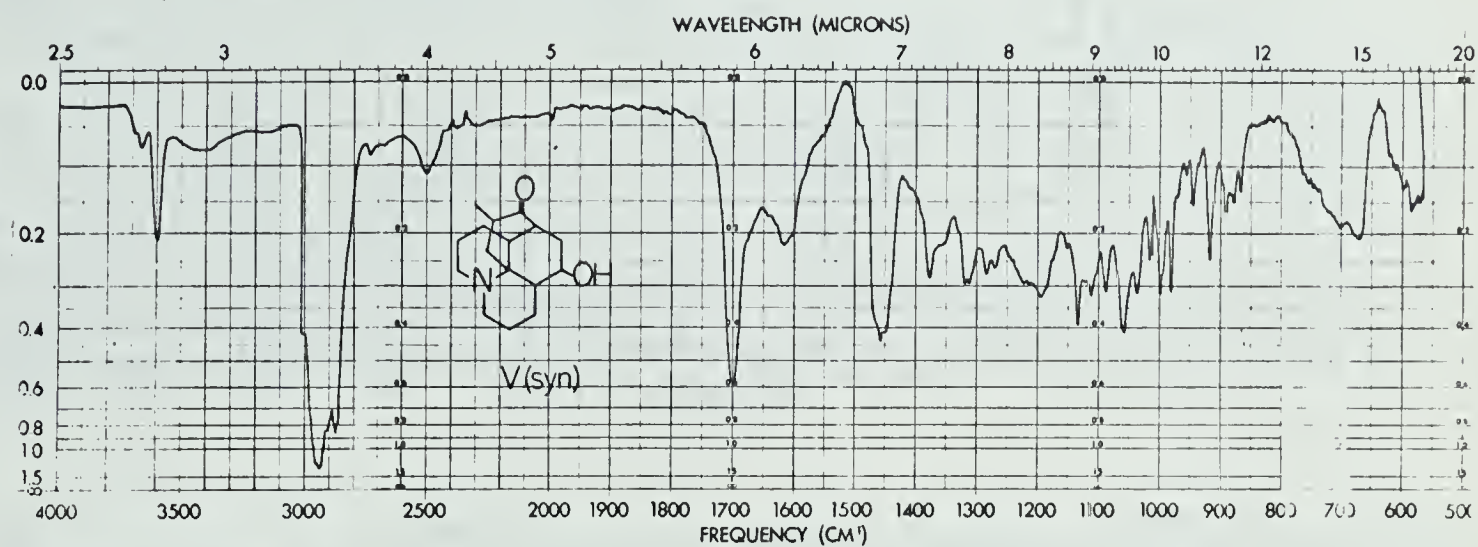


Figure 10

Figure 11

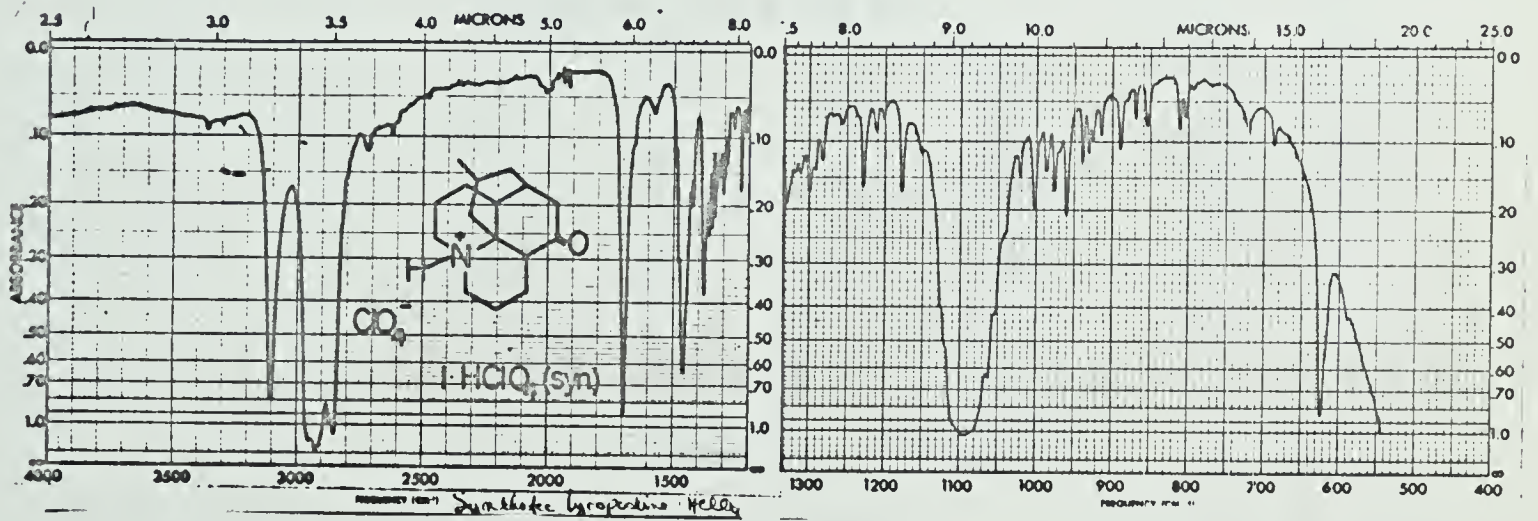
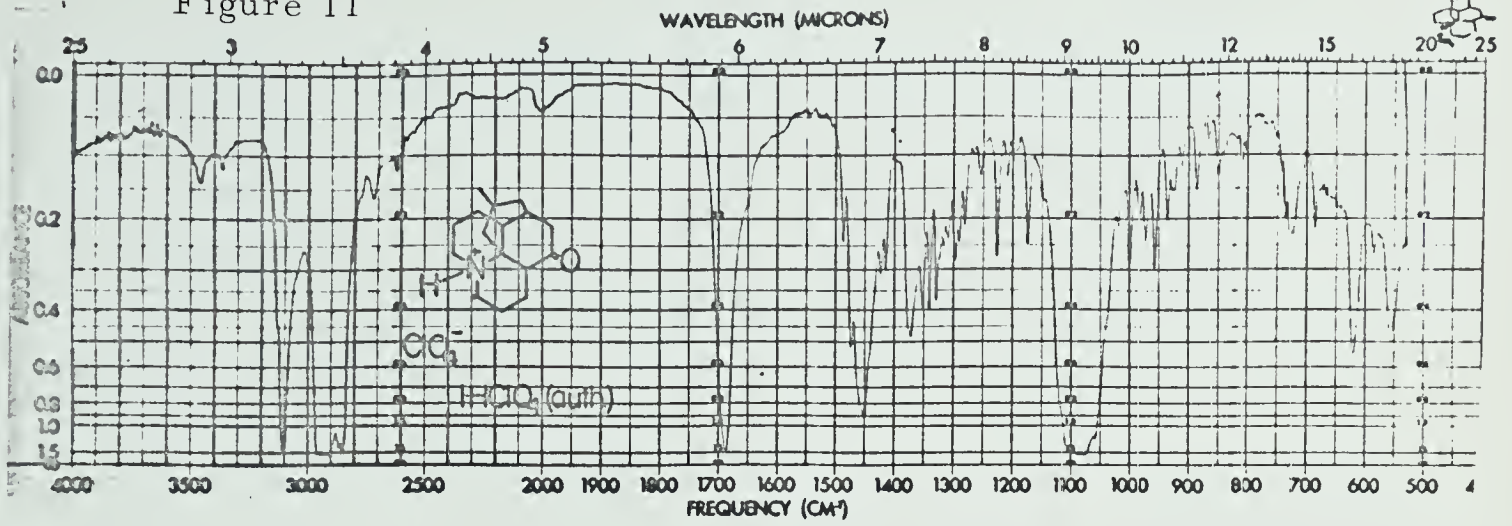


Figure 12

MASS SPECTRA

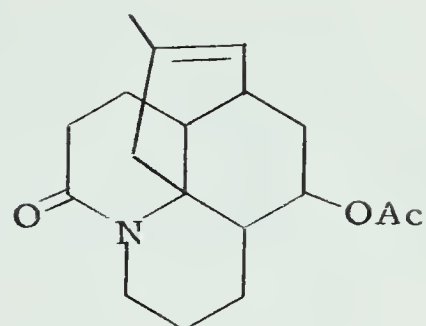
TABLE I

Unsaturated Amido Acetate LI

M.W. : 303

Temperature: 200°C

Electron Energy: 70 e.v.



LI

m/e	%B.P.	m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
304	1	202	23	160	14	120	13
303	11	200	23	152	17	108	10
302	56	189	12	151	60	105	15
244	52	188	59	150	13	93	12
243	100	187	14	134	11	91	29
242	13	186	19	133	10	79	18
228	53	175	10	132	22	77	21
		174	34	131	9		

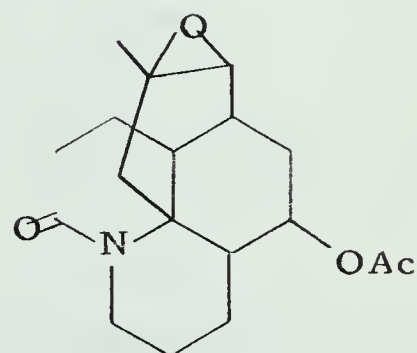
TABLE 2

8,15-Epoxy Lactam LVIII

M.W. : 319

Temperature: 200°C

Electron Energy: 70 e.v.



LVIII

m/e	% B.P.	m/e	% B.P.
319	10	160	13
302	11	151	11
249	19	134	11
248	28	132	18
190	20	91	11
189	48	77	10
188	100		

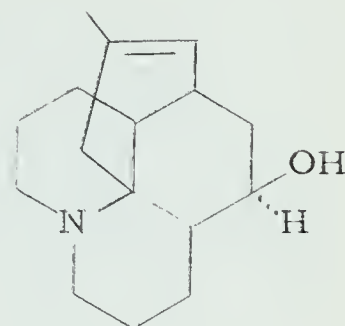
TABLE 3

 $\Delta^{8(15)}$ - β -Dihydrolycopodine LXXXVII

M.W. : 247

Temperature: 200°C

Electron Energy: 70 e.v.



LXXXVII

m/e	% B.P.	m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
248	11	192	28	161	14	122	26
247	60	191	11	160	41	120	25
246	15	190	30	148	14	91	31
232	29	189	8	146	36		
230	24	188	40	138	12		
229	22	186	20	137	100		
204	16	176	13	136	60		
203	26	175	15	135	11		
202	14	174	75	134	19		

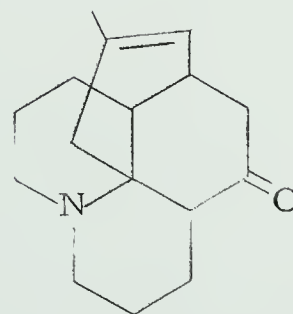
TABLE 4

8,15-Dehydrolycopodine LXXXVIII

M.W. : 245

Temperature: 185°C

Electron Energy: 70 e.v.



LXXXVIII

m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
246	17	189	12	134	11
245	100	188	22	91	16
244	11	174	20	77	13
230	17	160	48		
203	16	137	84		
202	27	136	30		
190	38	135	11		

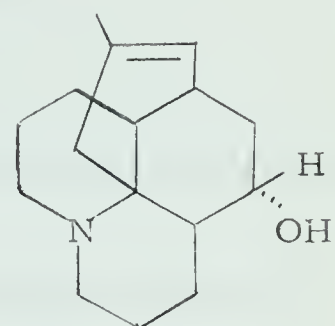
TABLE 5

$\Delta^{8(15)}$ - α -Dihydrolycopodine LXXXVI

M.W. : 247

Temperature: 200°C

Electron Energy: 70 e.v.



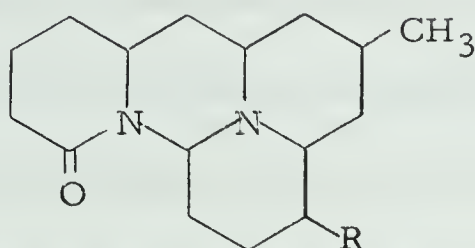
LXXXVI

m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
247	13	186	9	136	10
232	7	174	17	132	12
230	9	161	15	91	11
229	23	160	100	77	8
228	8	146	16		
203	7	145	11		
192	9	144	12		
188	9	137	18		

DISCUSSION AND RESULTS

C . THE TOTAL SYNTHESIS OF THE CERNUINE RING SKELETON

In 1964 Ayer and co-workers (15) published structural proposals for two new Lycopodium alkaloids cernuine (XI) and lycocernuine (XII). These alkaloids are novel in that they are the

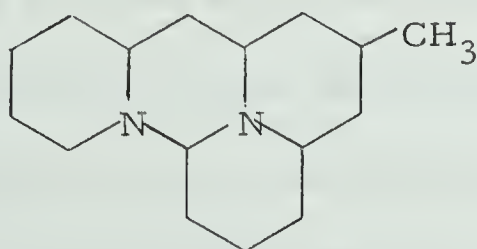


XI: $R = H$

XII: $R = OH$

only two Lycopodium alkaloids known to date which possess such a ring skeleton.

In order to confirm the structural assignment made for these alkaloids, we decided to attempt a synthesis of the cernuine ring skeleton as present in dihydrodeoxycernuine(XCIII)(no stereochemistry implied). Since the stereochemistry of cernuine was not



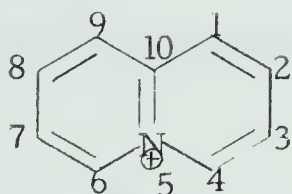
XCIII

known at the time that this work was begun, we were not initially aiming at a stereospecific synthesis of the alkaloids. We felt, however,

that if we could synthesize the gross cernuine ring skeleton XCIII we could confirm the structure by mass spectrometry. Since the mass spectra of stereoisomers usually do not differ markedly (53), the mass spectrum of a synthetic compound XCIII should be very similar to the mass spectrum of dihydrodeoxycernuine (XCIII), if the proposed structural skeleton is correct. Thus it was felt that even if no direct correlation between the natural and the synthetic series of compounds could be obtained, the structural assignment made for the alkaloids could be confirmed or disproved on the basis of the similarity or dissimilarity of the mass spectra of the natural and synthetic compounds. As will be seen later two of the synthetic compounds obtained were identical with compounds derived from the natural series and hence the structural skeleton proposed (15) for cernuine (XI) and lycocernuine (XII) must be correct. The fact that the synthetic and natural compounds are identical has proven useful in the elucidation of the stereochemistry of the alkaloids.

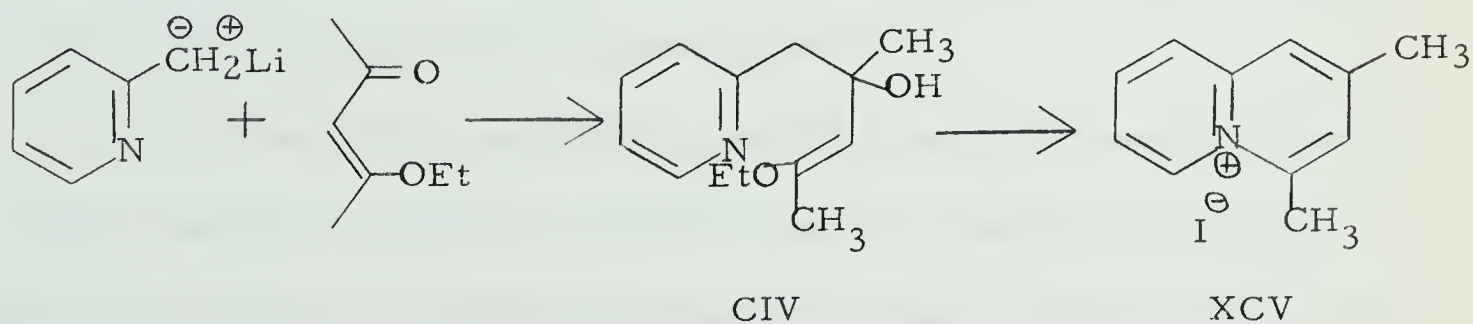
Although several different approaches to the total synthesis of the cernuine ring skeleton are possible, at the outset of the problem it was felt that, if successful, the use of quinolizinium salts as intermediates in the synthesis could lead to the desired result most directly.

Salts of the quinolizinium cation, which has the structure shown in XCIV, were first prepared in moderate yield by Boekelheide and co-workers (54). Richards and Stevens (56) have developed a more



XCIV

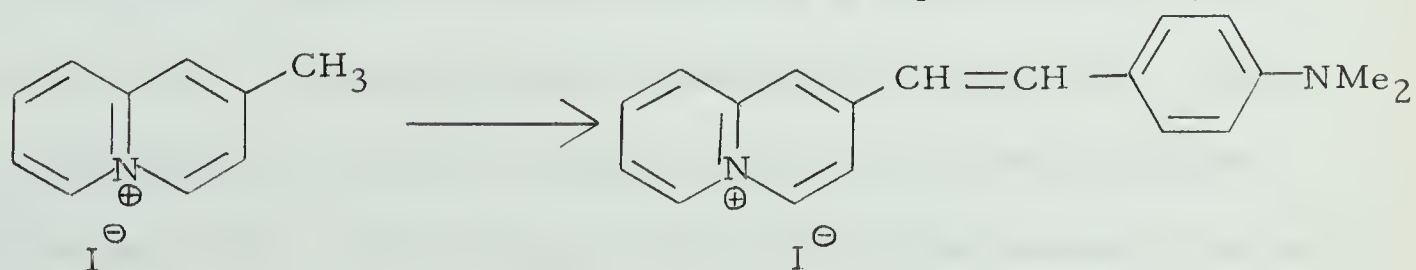
general method for preparing quinolizinium salts by extending the work of Woodward and McLamore (57). Thus by reacting a solution of picolyl lithium with the mono enol ether of 2,4-pentanedione (63) followed by treatment of the intermediate CIV with hydriodic acid, Richards and Stevens have prepared 2,4-dimethylquinolizinium iodide (XCV).



CIV

XCV

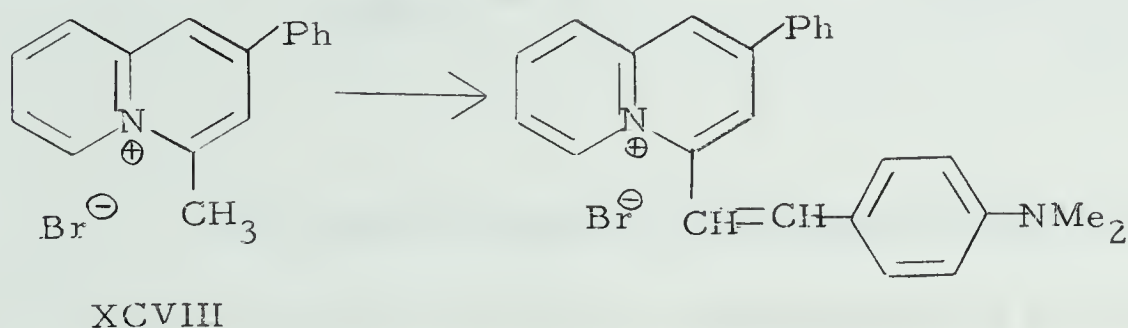
The condensation of some methylquinolizinium salts with benzaldehydes in the presence of base has been reported. Thus 2-methylquinolizinium iodide (XCVI) condenses with *p*-dimethylaminobenzaldehyde in the presence of piperidine to give the corresponding styryl derivative XCVII (56). Hansen and Amstutz (58) have reported that 2-phenyl-4-



XCVI

XCVII

methylquinolizinium bromide (XCVIII) also yields the corresponding styryl derivative XCIX with *p*-dimethylaminobenzaldehyde in the presence of piperidine.

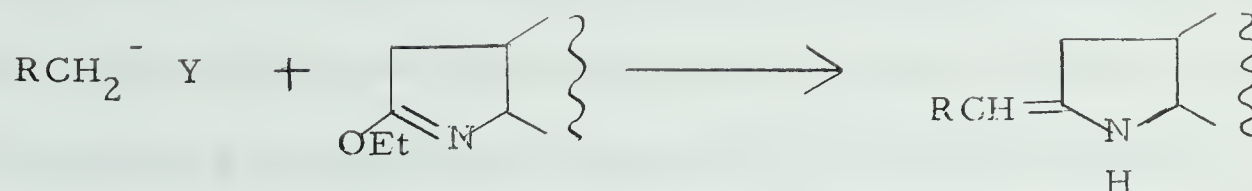


On the basis of the above observations it was hoped that if 2,4-dimethylquinolizinium iodide (XCV) was condensed with an electrophilic substrate that the product would be the result of condensation on the methyl group at C-4 rather than at C-2.

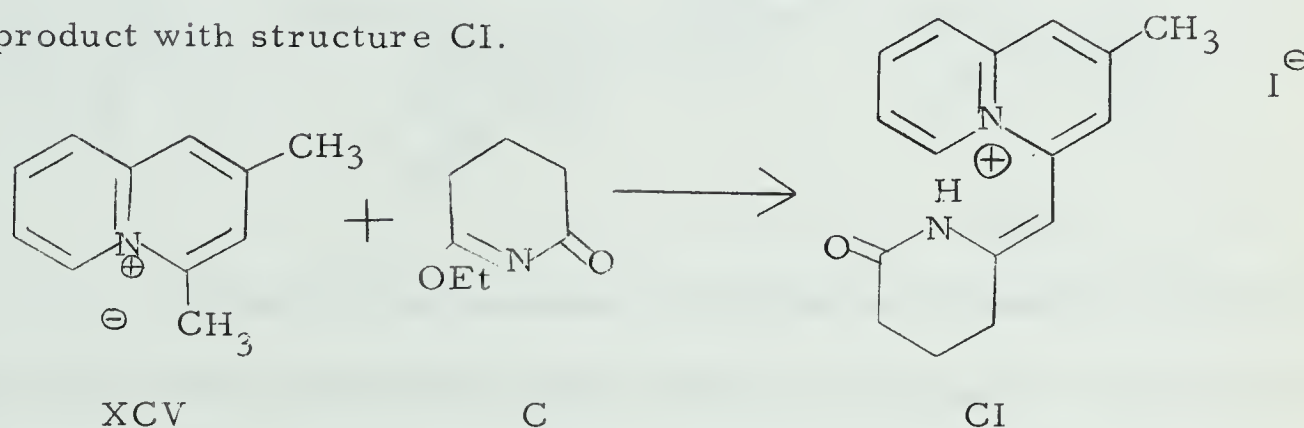
The protons on the C-4 methyl group presumably are more acidic than those on the C-2 methyl group since the C-4 methyl group is closer to the positively charged nitrogen. On the other hand steric factors favor condensation at the C-2 methyl group since the C-4 methyl group and the proton on C-6 are in close proximity to one another.

The increased reactivity of iminoester carbon toward nucleophilic reagents compared with that of amide carbon is well known (66). Iminoesters can be conveniently prepared (59, 60) by treatment of a secondary amide or lactam with triethyloxonium fluoborate (61). Eschenmoser (59, 60) has made extensive use of the fact that iminoesters add nucleophilic reagents in his synthesis of the

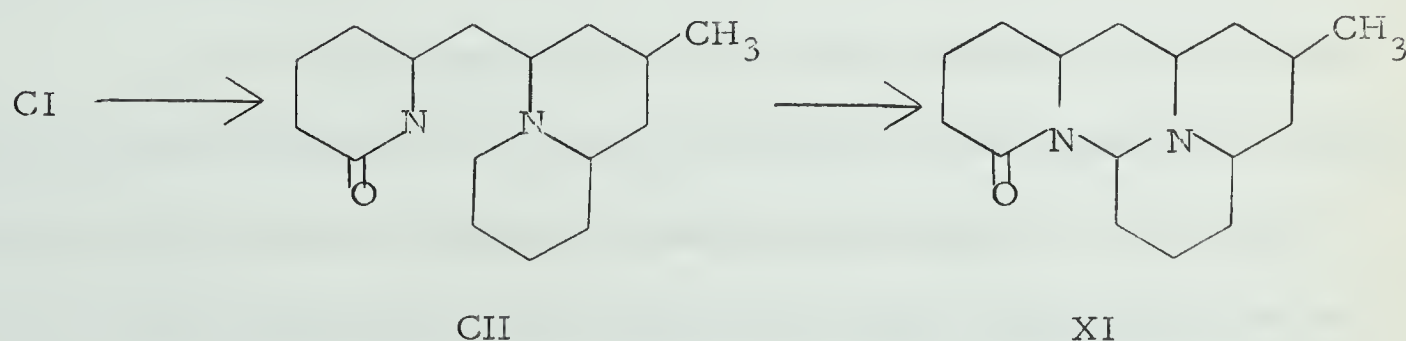
corrin system.



We hoped to condense 2,4-dimethylquinolinizinium iodide (XCV) with the mono-iminoester of glutarimide (C) in order to obtain a product with structure CI.

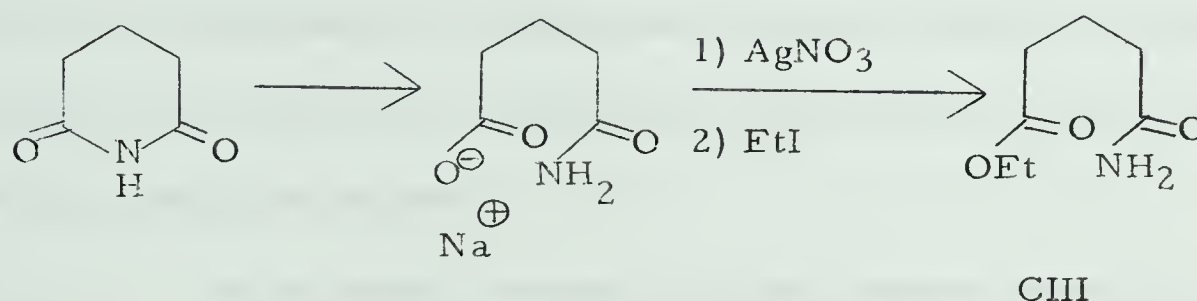


We then hoped to catalytically reduce CI to CII which perhaps on mercuric acetate oxidation could yield the cernuine (XI) skeleton.



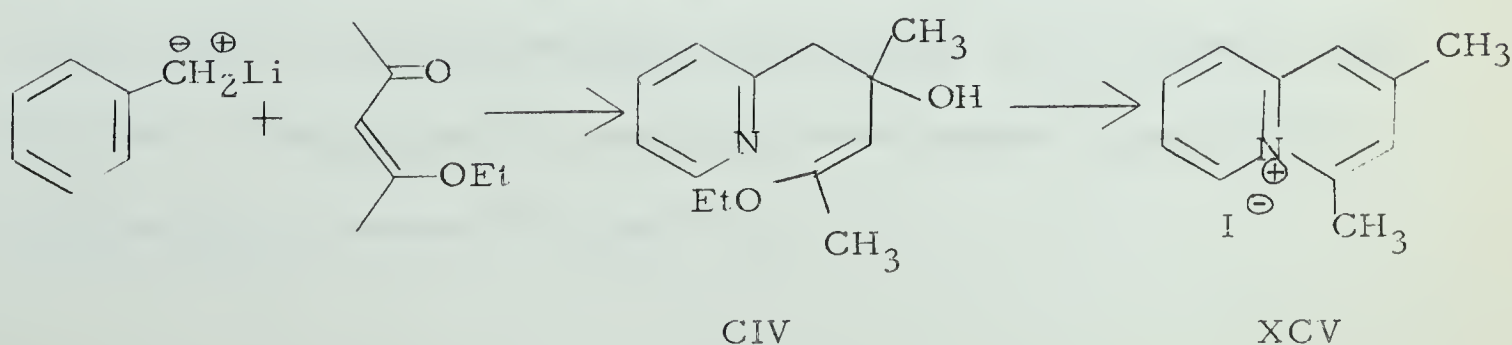
Unfortunately we were unable to prepare the iminoester C of glutarimide. Treatment of glutarimide (62) with triethyloxonium fluoborate over a wide range of conditions invariably led to recovery of starting material.

When a sodium hydroxide solution of glutarimide was treated with silver nitrate followed by reaction of the salt so obtained with ethyl iodide (65) a good yield of the monoethyl ester CIII was obtained. Presumably glutarimide was hydrolyzed by the sodium hydroxide to the monoamide of glutaric acid, the silver salt of which was esterified with ethyl iodide to yield the monoester monoamide CIII.



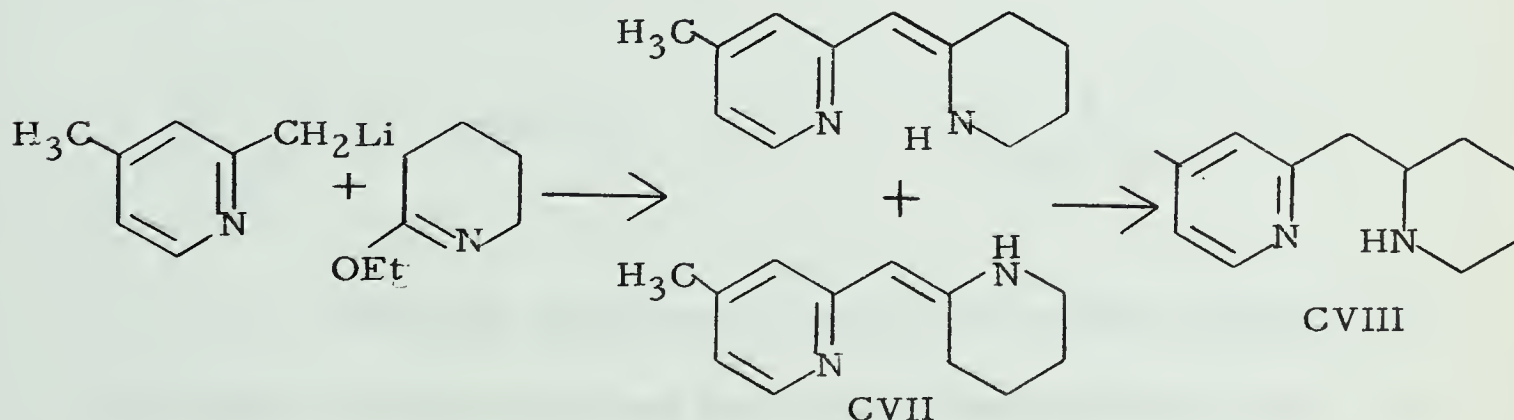
Following the procedure described by Richards and Stevens (56) 2,4-dimethylquinolinizinium iodide (XCV) was prepared in good yield. Condensation of picolyl lithium with the enol ether of 2,4-pentanedione gave the basic enol ether CIV which on treatment with hydriodic acid gave the iodide XCV.

The N.M.R. spectrum of the salt in ethylene carbonate had three proton singlets at τ 7.3 and τ 6.9 for the 2-methyl and the 4-methyl signal respectively and had six aromatic protons between τ 0.5 and τ 2.0. In trifluoroacetic acid solution the methyl signals appeared at τ 7.6 and τ 7.3.

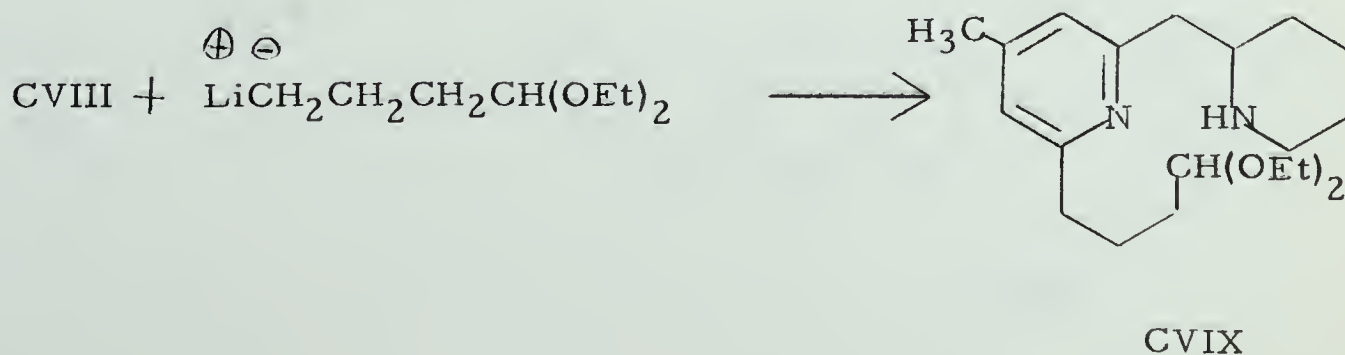


When it was found that condensation of the quinolizinium salt XCV with the aldehyde had occurred on the C-2 methyl group rather than on the C-4 methyl group, this approach to the synthesis of cernuine ring skeleton was abandoned.

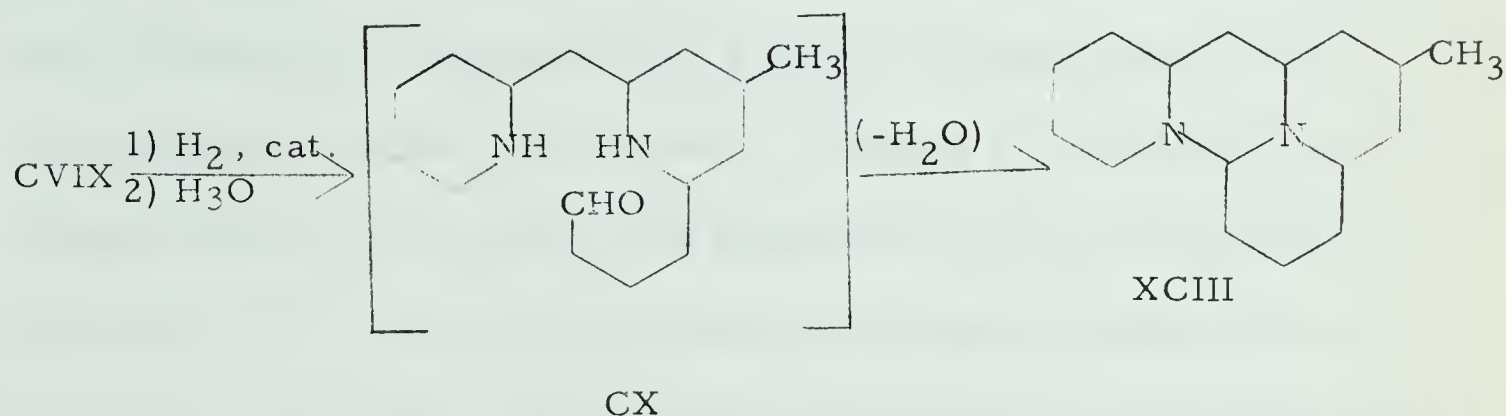
A second possible approach to the synthesis of the cernuine ring skeleton was then investigated. It was hoped that condensation of the monolithium salt of 2,4-lutidine with the iminoester (CVI) of valerolactam would yield the olefinic intermediate CVII which on catalytic hydrogenation would yield 2-(2-piperidylmethyl)-4-methylpyridine (CVIII). Since the addition of alkyl lithium compounds to the azomethine linkage of pyridines is a well known reaction (68), it was hoped that



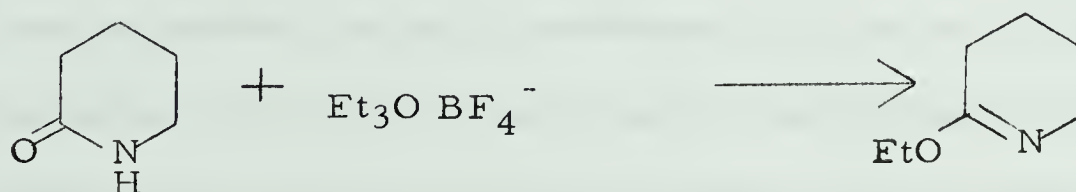
alkylation of the piperidylpyridine CVIII with the lithium salt of γ -bromobutyraldehyde diethylacetal would yield the trisubstituted pyridine CVIX. Hydrogenation of the pyridine ring in CVIX followed



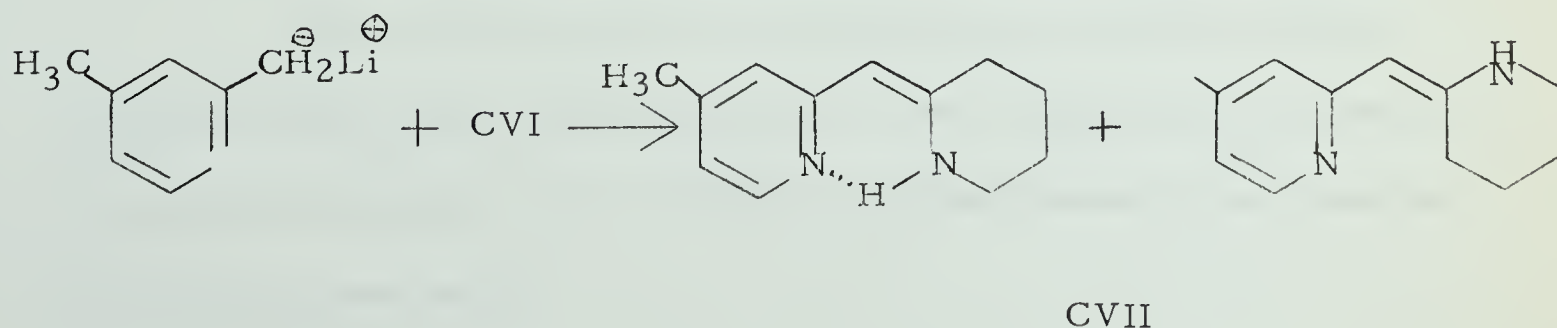
by acid hydrolysis of the acetal function would yield the dipiperidyl aldehyde CX which on ring closure should yield the cernuine ring skeleton XCIII.



The iminoester of valerolactam (CVI) was prepared in high yield by treatment of valerolactam with triethyloxonium fluoborate in methylene chloride solution.

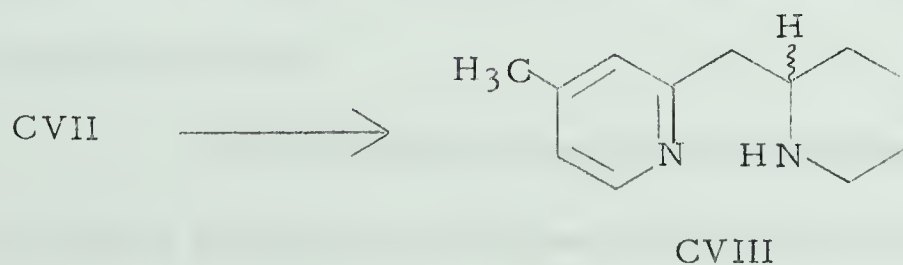


When the monolithium salt of 2,4-lutidine, prepared by stirring 2,4-lutidine with one equivalent of phenyllithium (64), was reacted with the iminoester (CVI) of valerolactam the product, after chromatography, appeared to be a mixture of the two double bond isomers CVII. The infrared spectrum contained an N-H stretching



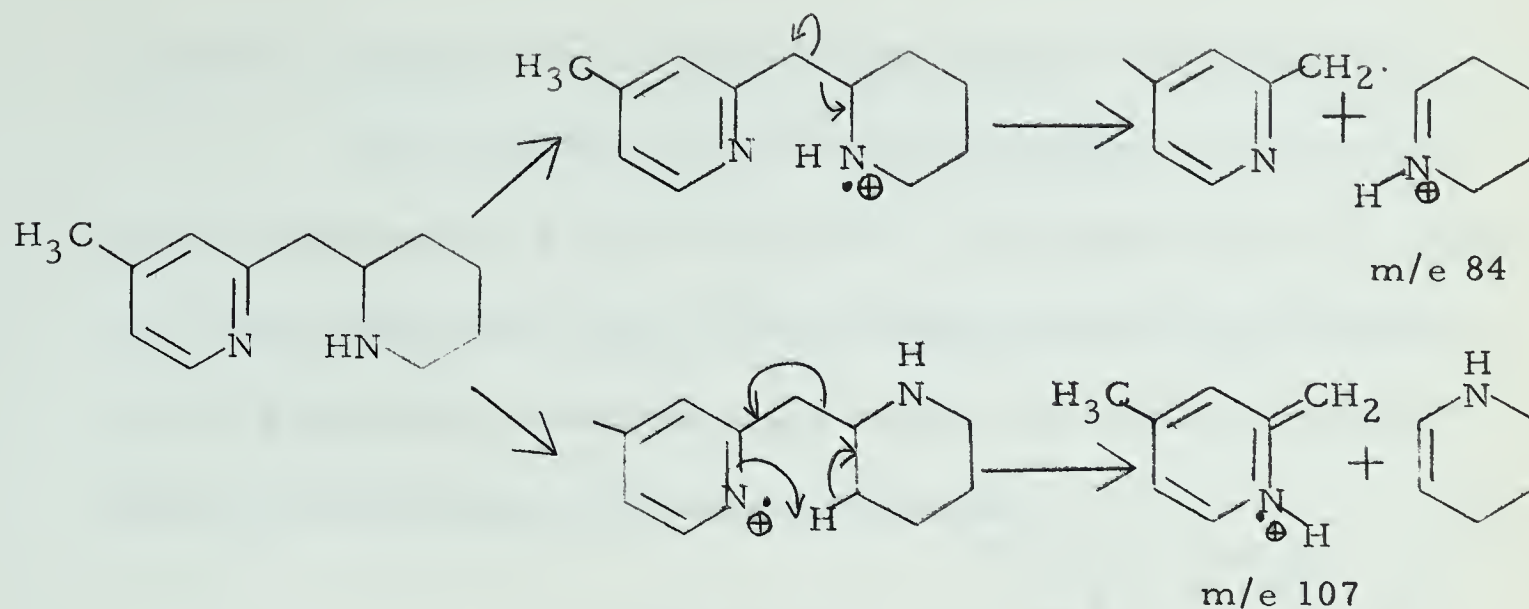
band at 3200 cm^{-1} and had three sharp strong bands at 1610, 1600 and 1550 cm^{-1} attributed to the unsaturated system present in CVII. The N.M.R. spectrum indicated the presence of the two double bond isomers as it contained two singlets at τ 7.8 and τ 7.7 (ratio about 2:1) for two different aromatic methyl groups. Signals at τ 5.15 and τ 0.5 (broad) totalling one proton which disappeared on D_2O exchange are attributed to the non-hydrogen bonded and hydrogen-bonded proton on nitrogen respectively. The aromatic proton alpha to the nitrogen atom also appeared as a pair of doublets at τ 1.8 and τ 1.65 indicating the presence of two isomeric compounds.

Hydrogenation of the mixture of double bond isomers CVII over palladium-charcoal at atmospheric pressure resulted in the formation of a single product to which was assigned the structure CVIII. The formation of only one product from a mixture of two compounds is consistent with the hydrogenation of the double bond



in CVII thus removing the possibility of double bond isomerism.

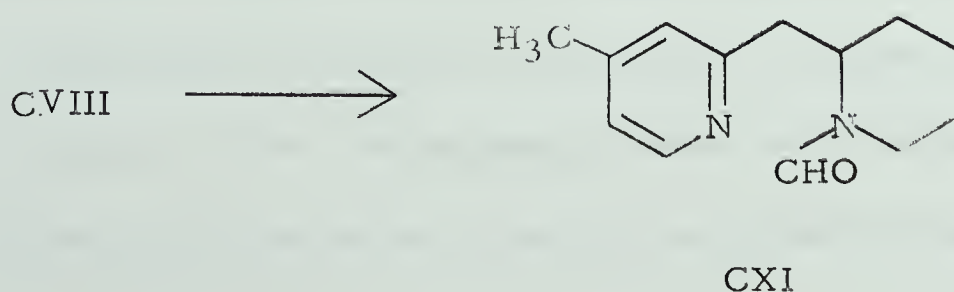
The mass spectrum of 2-(2-piperidylmethyl)-4-methylpyridine (CVIII) had a parent peak at m/e 190 as expected and contained two prominent peaks at m/e 107 and m/e 84 attributed to ions with the structures shown below.



Concentration independent absorption at 3320 cm^{-1} in the infrared spectrum of CVIII revealed the presence of an intramolecularly hydrogen bonded N-H function and absorption bands at 3060 , 3020 and 1600 cm^{-1} confirmed the presence of the aromatic portion of the molecule.

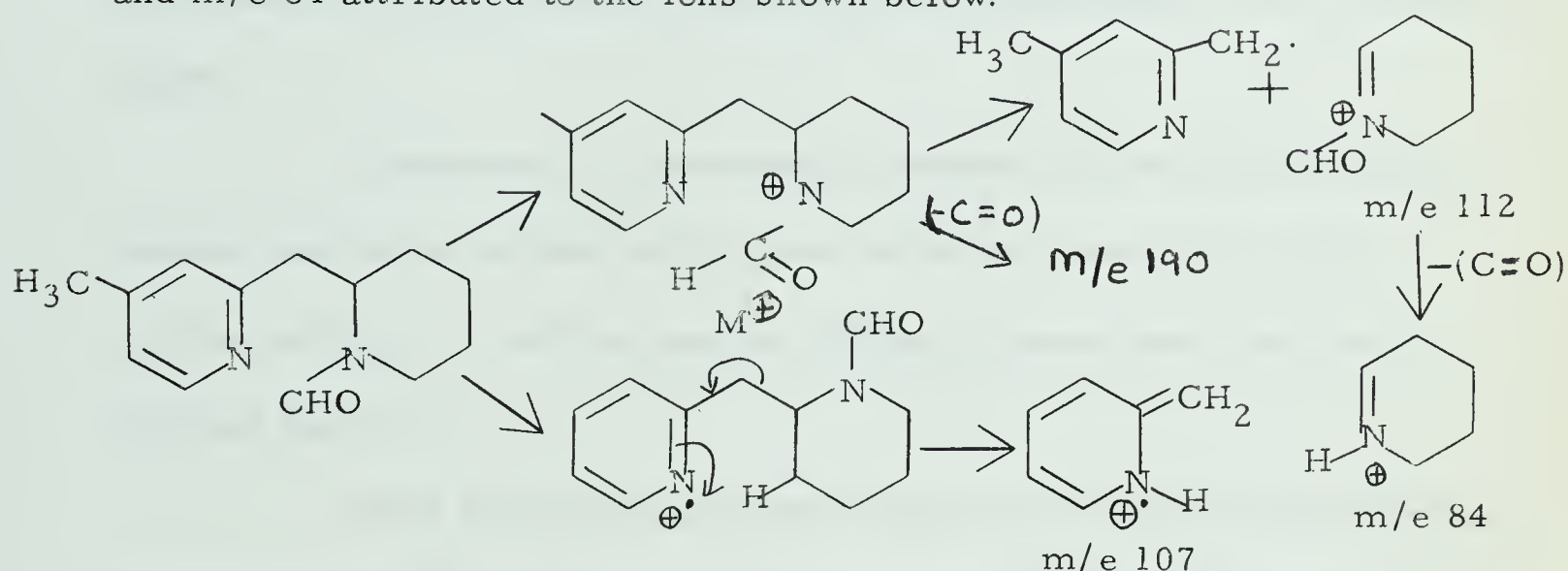
The N.M.R. spectrum displayed a singlet at τ 7.7 for the aromatic C-methyl group, as well as a two proton signal between τ 2.5 and τ 3.0 and a one proton doublet at τ 1.5 for the three aromatic protons.

Formylation of the piperidylpyridine CVIII according to the procedure described by Huffman (67) yielded the corresponding N-formyl compound CXI. This step was necessary in order to protect the



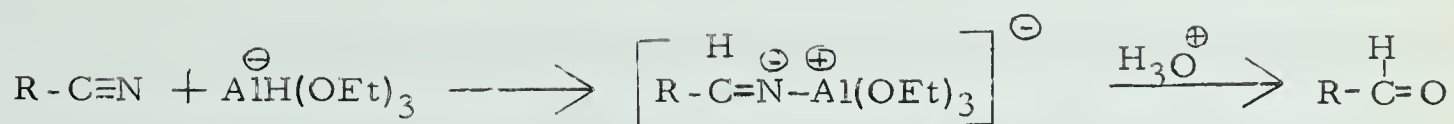
secondary nitrogen atom in CVIII for the proposed alkylation step.

The formation of the N-formyl compound was indicated by the appearance of a band at 1665 cm^{-1} in the infrared spectrum and was confirmed by the mass spectrum which now had a parent peak at m/e 218 with other prominent peaks at m/e 190, m/e 112, m/e 107 and m/e 84 attributed to the ions shown below.



Hydrolysis of the N-formyl compound CXI in either acidic or basic media regenerated the piperidylpyridine CVIII in high yield, assuring easy removal of the blocking group once its task had been completed.

Having synthesized the desired pyridine compound CXI, we now turned our attention to the synthesis of γ -bromobutyraldehyde diethyl acetal. Recently Brown and co-workers (69) have reported a convenient method for preparing aldehydes from nitriles. They have obtained good yields of a wide variety of aldehydes by the partial reduction of the corresponding nitrile with lithiumtriethoxyaluminumhydride followed by acid hydrolysis of the intermediate salt.

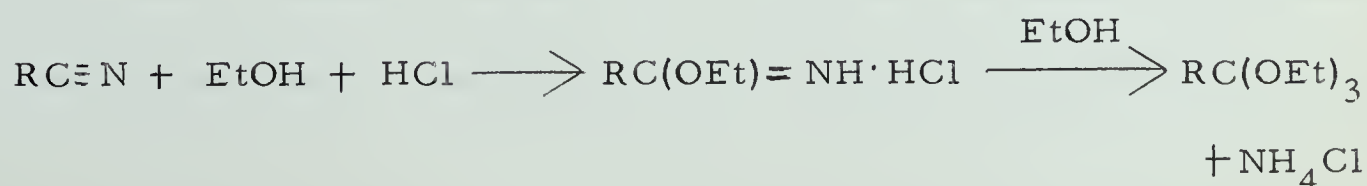


When, however, γ -bromobutyronitrile was reacted under the conditions described by Brown (69) none of the expected γ -bromobutyraldehyde was obtained. Instead the starting nitrile was recovered intact.

Treatment of γ -bromobutyronitrile with one equivalent of lithium aluminum hydride at 0°C also failed to furnish any of the desired aldehyde. In this case the product obtained was also mainly starting material.

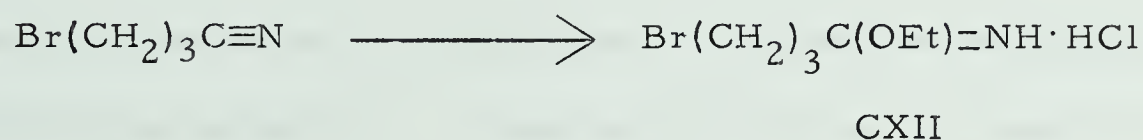
When γ -bromobutyronitrile was reacted under the conditions of the Stephens reduction (70) again none of the desired γ -bromobutyraldehyde was obtained.

The preparation of aldehyde acetals by the lithium aluminum hydride reduction of the corresponding orthoester was reported in 1951 (71). A method for converting nitriles into orthoesters has been described by McElvain and Nelson (72). These workers modified the procedure originally developed by Pinner (73) who reported the isolation of orthoesters by alcoholysis of iminoester hydrochlorides which in turn were prepared from nitriles. These reactions are shown below.



McElvain and Nelson found that by carrying out the alcoholysis of the iminoester hydrochloride in a refluxing ether solution the reaction time was cut from fourteen days to less than twenty-four hours and the yields of the orthoester were substantially increased over those obtained by Pinner.

When γ -bromobutyronitrile was reacted with one equivalent of absolute ethanol and one equivalent of dry hydrogen chloride the corresponding iminoester hydrochloride CXII was obtained as a colorless solid in high yield. The salt had strong infrared absorption in Nujol



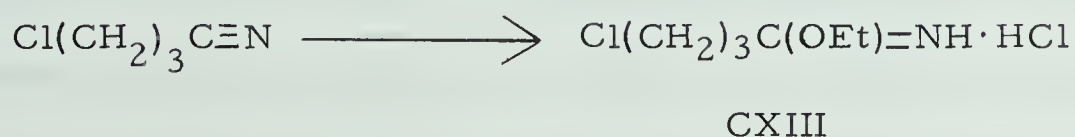
between 3200 and 2600 cm^{-1} as well as a strong band at 1645 cm^{-1} as expected.

It was hoped that alcoholysis of the iminoester hydrochloride with absolute ethanol in a refluxing ether solution would yield the triethylorthoester of γ -bromobutyric acid. The product obtained from this reaction however appeared to be badly contaminated with the normal carboxylic ester, ethyl γ -bromobutyrate, as indicated by a strong band in the infrared spectrum at 1730 cm^{-1} . The orthoester appeared to undergo hydrolysis during the removal of the solvents since the band at 1730 cm^{-1} in the infrared spectrum of the product increased in intensity as more of the solution containing the orthoester was concentrated. Perhaps a small amount of hydrobromic acid was

being eliminated from the orthoester during removal of the solvents, thus catalyzing the hydrolysis of the orthoester. Distillation under reduced pressure failed to provide any of the pure orthoester. Attempted removal of the carboxylic ester by alkaline hydrolysis of the mixture was also unsuccessful as the product obtained from such treatment still exhibited a strong band at 1730 cm^{-1} in the infrared spectrum.

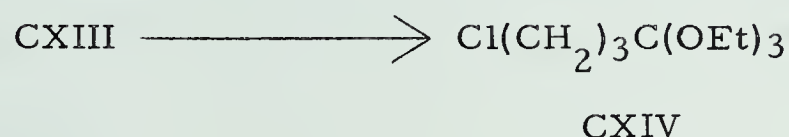
Thus it became apparent that the orthoester of δ -bromobutyric acid was extremely easily hydrolyzed to the carboxylic ester and when it was found that the orthoester could not be obtained in reasonably pure form we decided to try to prepare the diethylacetal of δ -chlorobutyraldehyde. Though alkyl chlorides are generally less reactive towards lithium metal than the corresponding bromide, it has been reported (74) that aliphatic chlorides are preferred to bromides for reaction with lithium. With this thought in mind we set about to prepare δ -chlorobutyraldehyde diethylacetal.

Reaction of γ -chlorobutyronitrile with absolute ethanol and dry hydrogen chloride resulted in the formation of a nearly quantitative yield of the expected iminoester hydrochloride CXIII which, like



the bromo compound CXII, had strong infrared absorption between 3200 and 2600 cm^{-1} in addition to a strong band at 1645 cm^{-1} .

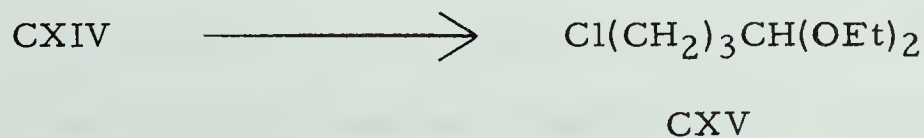
Alcoholysis of the iminoester hydrochloride with absolute ethanol in a refluxing ether solution gave a high yield of the triethyl-orthoester of γ -chlorobutyric acid CXIV which was contaminated with only a trace of carbonyl containing impurity. By stirring the crude product with aqueous alcoholic potassium hydroxide the carbonyl containing impurity was removed and the pure orthoester was obtained.



The chloroorthoester so prepared had intense infrared absorption between 1050 and 1100 cm^{-1} attributed to the carbon-oxygen stretching vibrations.

The N.M.R. spectrum of the orthoester had a nine proton triplet at τ 8.8 and a six proton quartet at τ 6.5 which was superimposed on a two proton signal due to the protons bonded to the carbon carrying the chlorine. A four proton signal at τ 8.2 was attributed to the protons on the two in-chain methylene units of the orthoester.

Lithium aluminum hydride reduction of chloroorthoester gave the desired chlorobutyraldehyde diethylacetal (CXV) in high yield. Treatment of the acetal with 2,4-dinitrophenylhydrazine reagent converted it to the 2,4-dinitrophenylhydrazone of γ -chlorobutyraldehyde.



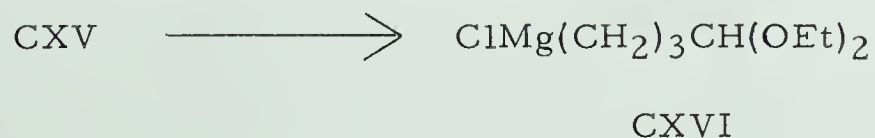
The infrared spectrum of the acetal contained the expected

strong bands at 1130 cm^{-1} and 1070 cm^{-1} due to the carbon-oxygen stretching vibrations.

The N.M.R. spectrum of the chloroacetal had a six proton triplet at τ 8.8, a four proton signal centered at τ 8.25, a six proton multiplet at τ 6.4 due to the the two methylene units attached to oxygen and the methylene unit carrying the chlorine atom, and a one proton triplet at τ 5.5 due to the proton on the carbon carrying the two alkoxy functions.

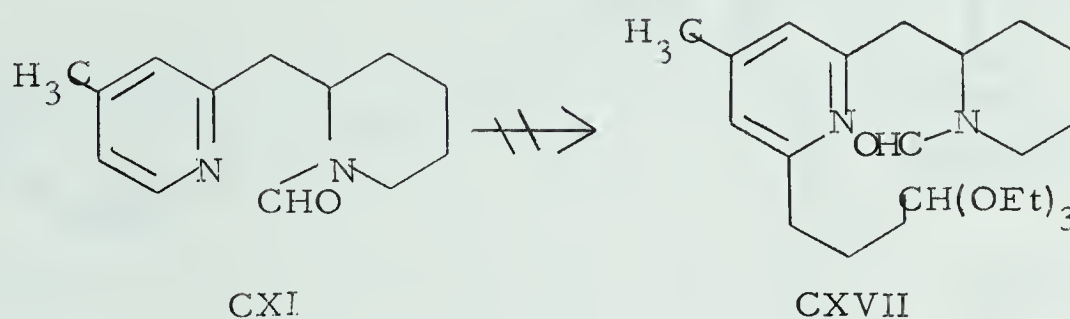
We were now ready to prepare the alkyllithium salt from γ -chlorobutyraldehyde diethylacetal. However when finely divided lithium was stirred with the chloroacetal CXV in either anhydrous ether, dry isopentane or dry petroleum ether no reaction was observed. In every case the lithium metal was not consumed and the chloroacetal could be recovered in quantitative yield.

However when the chloroacetal CXV was reacted with magnesium metal in refluxing dry tetrahydrofuran using a small amount of methyl iodide to trigger the reaction, all of the magnesium was consumed within eight hours.



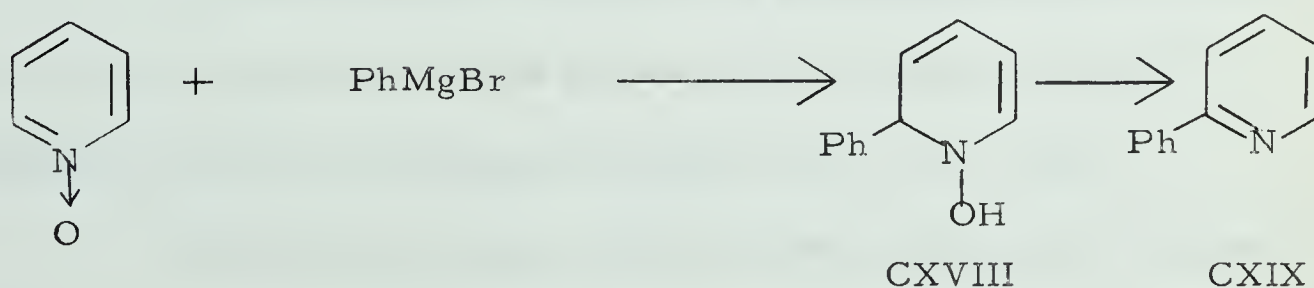
Condensation of the Grignard reagent CXVI with the N-formyl piperidylpyridine (CXI) followed by oxidation of the crude product with a slow stream of air and removal of the low boiling components by

vacuum distillation yielded a viscous black tarry substance which displayed at least five spots on thin layer chromatography. None



of the hoped for condensation product CXVII could be obtained from this mixture.

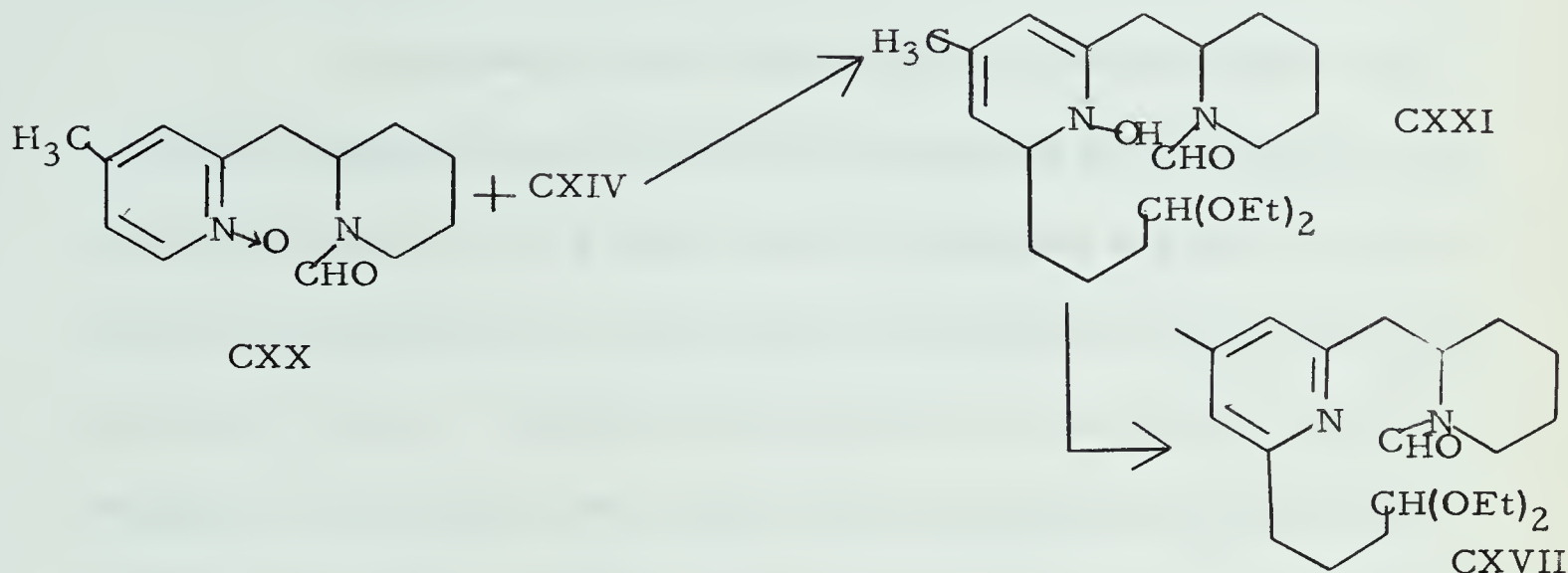
At this time a publication (76) appeared describing the reaction of pyridine and quinoline N-oxides with phenyl magnesium bromide. Thus a high yield of 2-phenylpyridine CXIX was obtained from the reaction of pyridine-1-oxide with phenyl magnesium bromide followed by dehydration of the intermediate 1,2-dihydro compound with acetic anhydride. In this way good yields of 2-phenyl-6-methyl pyridine and 2-phenyl-4-methyl pyridine were also obtained from



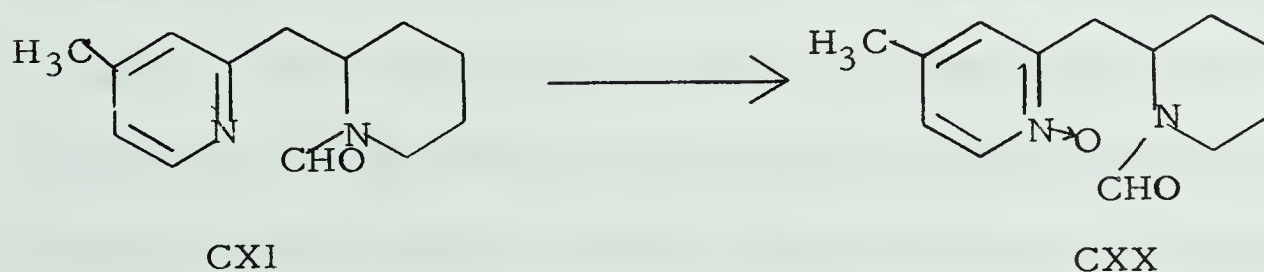
2-picoline-1-oxide and 4-picoline-1-oxide respectively.

In our synthetic series, treatment of the pyridine N-oxide CXX with the Grignard reagent CXVI should give the intermediate

dehydro compound CXXI which on dehydration would give the desired product CXVII with the side-chain attached.



Reaction of the N-formyl piperidylpyridine (CXI) with m-chloroperbenzoic acid (77) converted it to the corresponding N-oxide CXX which showed only one spot on thin layer chromatography, more polar than the starting material.



The fact that the N-oxide CXX had formed was indicated by the infrared spectrum which had an intense band at 1240 cm^{-1} attributed to the N-O stretching vibration (ref. 77, p. 120).

The mass spectrum of the N-oxide did not show a parent peak and was nearly identical with that of the starting material CXI. The fact that the N-oxide did not show a parent peak in the mass spectrum was not surprising since under heated inlet conditions most N-oxides

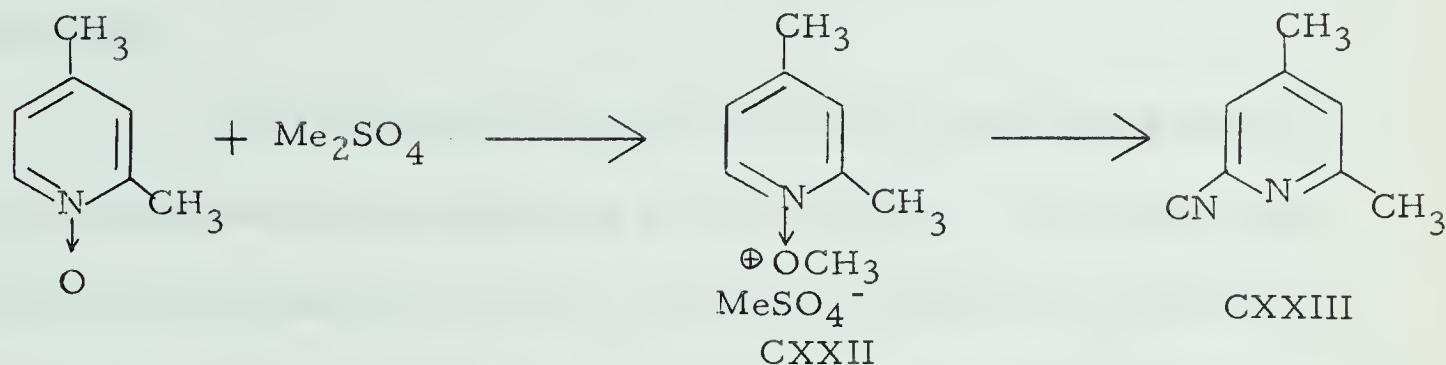
lose oxygen very rapidly and show intense M-16 peaks rather than parent peaks (78).

Treatment of the N-oxide CXX with one equivalent of the Grignard reagent prepared from the chloroacetal CXV resulted in the immediate formation of a thick creamy precipitate and after stirring at room temperature for sixteen hours the pyridine N-oxide CXX was recovered intact. The immediate formation of the thick precipitate suggested that perhaps the N-oxide CXX was hydrated and that upon addition to the Grignard reagent immediate hydrolysis of the reagent took place.

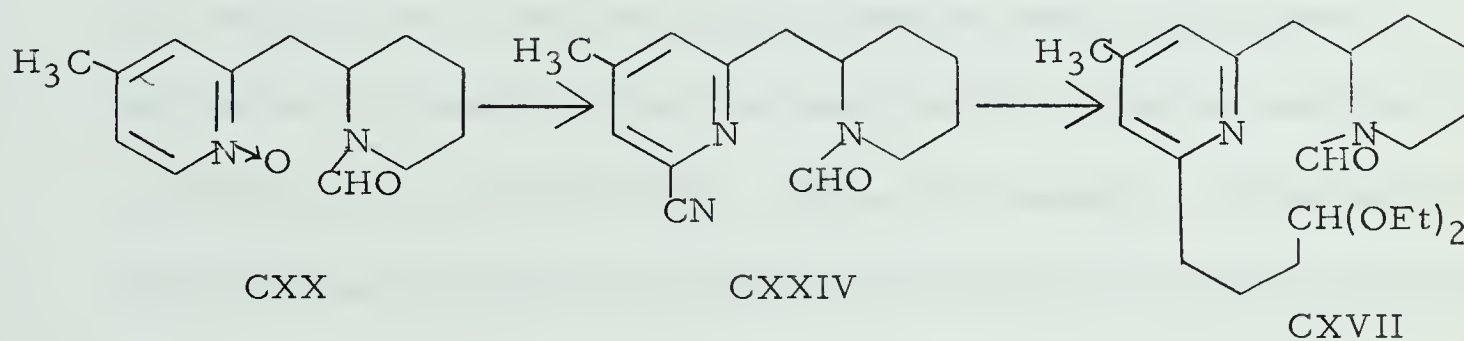
Attempts to dry the N-oxide CXX prior to the reaction with the Grignard reagent failed to improve the results obtained. Finally the N-oxide was reacted with a large excess of the Grignard reagent. After removal of the low boiling components of the reaction mixture by vacuum distillation the residue consisted of a viscous dark brown oil which showed no distinct spots on thin layer chromatography but ran as a single streak all the way up the chromatogram. Neither column chromatography of the oil nor acid-base extraction furnished any characterizable materials.

In 1959 Feely and Beavers (79) reported a new preparation of cyanopyridines by the cyanation of pyridine oxide salts. These workers found for example that treatment of 2,4-lutidine N-oxide with dimethyl sulfate converted it to the corresponding O-methyl salt CXXII

which on treatment with cyanide ion in aqueous solution at room temperature gave a good yield of 2-cyano-4,6-dimethylpyridine CXXIII.



We felt that if we could prepare the cyano derivative CXXIV from the N-formyl piperidylpyridine N-oxide (CXX) we might then be able to prepare the product CXVII which has the required side chain.

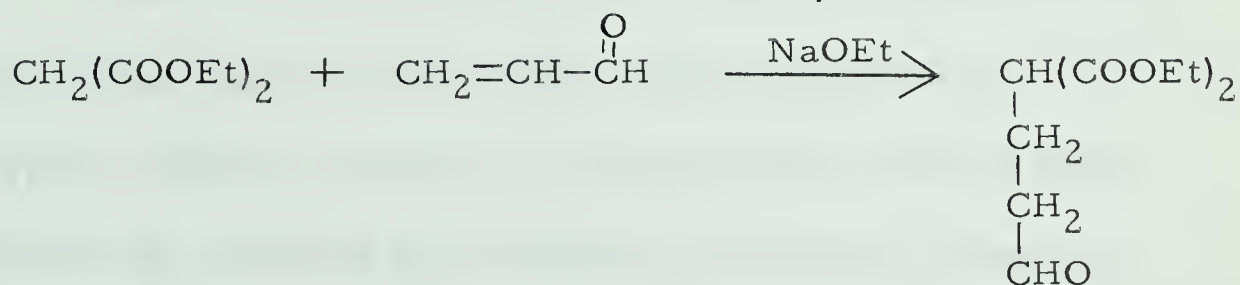


Treatment of the pyridine N-oxide CXX with dimethyl sulfate resulted in the formation of a semi-solid gum which was not isolated but dissolved immediately in water. Addition of potassium cyanide to the aqueous solution and stirring the resulting solution at room temperature for six hours gave a brown oil which was made up of at least five components as indicated by thin layer chromatography. The infrared spectrum of the crude product did not show any trace of nitrile absorption.

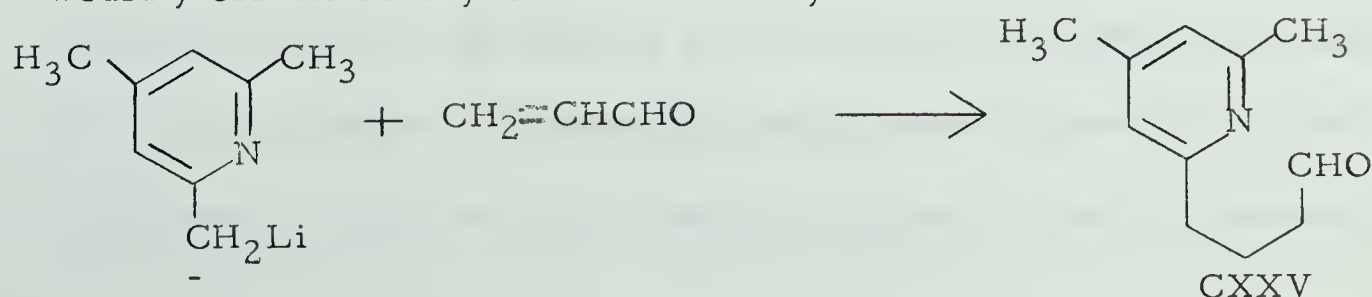
With the failure of this method to introduce a nitrile group into the pyridine ring of CXX we decided to try a slightly modified

approach to the synthesis of the cernuine skeleton in which we would attach the desired side-chain to the pyridine nucleus early in the synthesis.

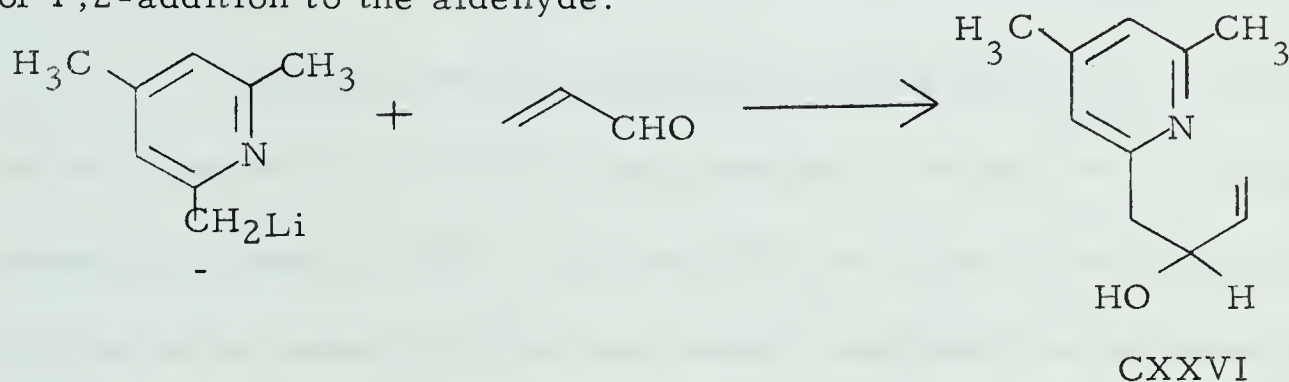
The starting point for the third approach to the synthesis of the cernuine ring skeleton was 2,4,6-collidine. The preparation of the monolithium salt of 2,4,6-collidine by reaction of the base with one equivalent of phenyllithium has been reported by Cale and co-workers (64). These authors have shown that the monolithium salt is formed exclusively at the 2-position of 2,4,6-collidine. It has been reported that condensation of α,β -ethylenic aldehydes with suitable acid derivatives (malonates, cyanoacetates) results in Michael addition of the nucleophile to the aldehyde (80). Thus, for example, condensation of the sodium salt of diethyl malonate with acrolein (81) yields the product of 1,4-addition (or Michael addition) to the aldehyde.



On the basis of the above observations it was hoped that condensation of the monolithium salt of 2,4,6-collidine with acrolein would yield the aldehyde CXXV directly.



In fact when the monolithium salt of 2,4,6-collidine was prepared and condensed with acrolein the major product obtained was not the hoped for product of Michael addition to the α, β -unsaturated aldehyde but instead was the unsaturated alcohol CXXVI, the product of 1,2-addition to the aldehyde.

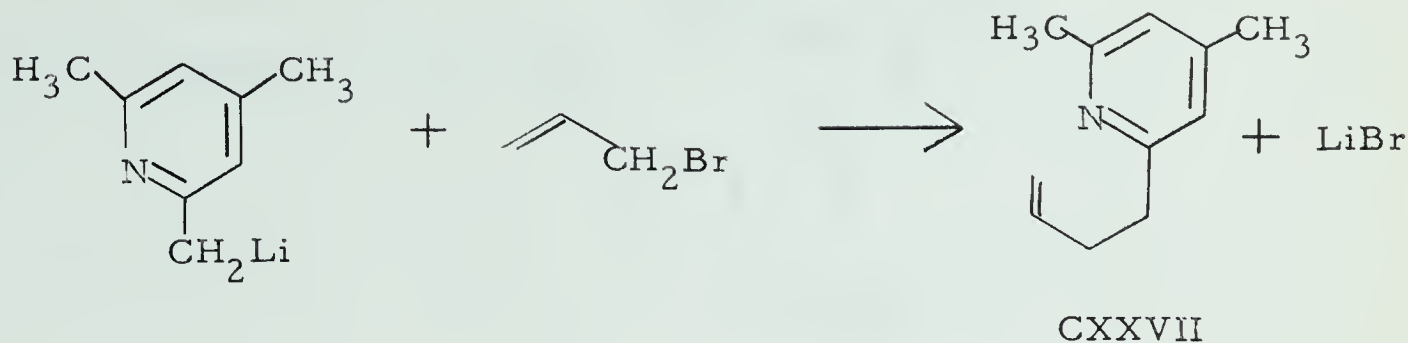


That the alcohol CXXVI and not the aldehyde CXXV had formed was evident from both the infrared and N.M.R. spectrum of the crude product. The infrared spectrum contained hydroxyl absorption at 3600 cm^{-1} and did not show any carbonyl absorption.

The N.M.R. spectrum of the crude product showed an aromatic proton signal at $\tau 3.2$ and a signal between $\tau 4.0$ and $\tau 5.2$ in the typical pattern of protons on a vinyl group. No low field signal due to the presence of an aldehydic proton was observed.

Since condensation of the collidyllithium with acrolein did not give the desired product CXXV, we were forced to elaborate the side chain by a less direct method. In 1931 Wilkinson (83) reported the preparation of Δ^1 -olefins by the alkylation of Grignard reagents with allyl bromide. Condensation of the monolithium salt of 2,4,6-collidine with allyl bromide would be expected to give 2-(3-butenyl)-

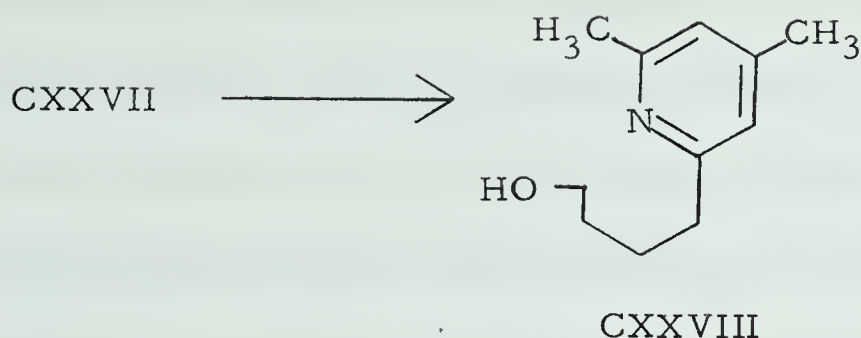
-4,6-dimethylpyridine (CXXVII).



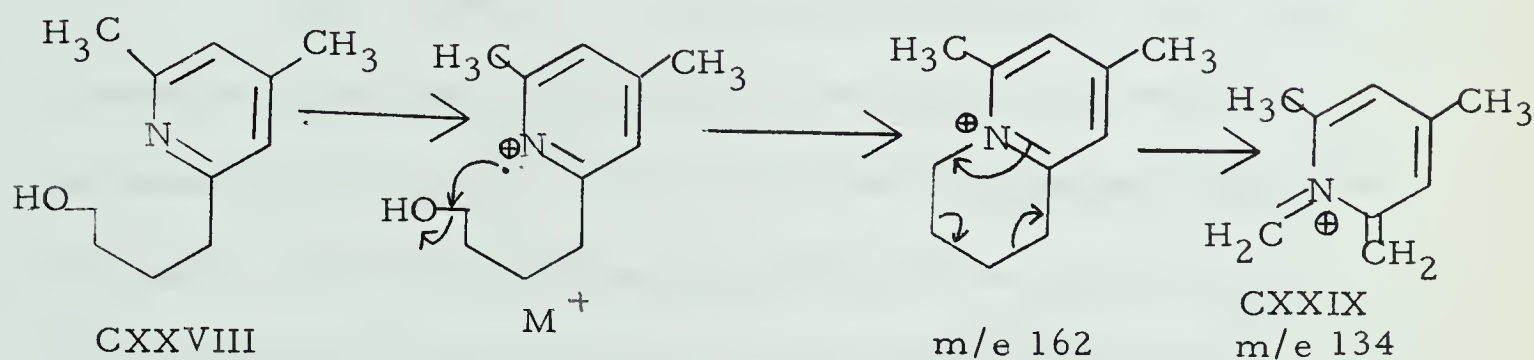
Indeed when the condensation was carried out a high yield of the expected olefin CXXVII was obtained. In addition to infrared absorption bands at 3020, 1610 and 1550 cm^{-1} due to the aromatic portion of the molecule, the unsaturated compound had infrared bands at 3080, 1645, 990 and 910 cm^{-1} attributed to the presence of the vinyl group.

The N.M.R. spectrum of the olefin had two singlets at $\tau 7.75$ and $\tau 7.5$ for the two methyl groups present in CXXVII, a four proton signal between $\tau 7.0$ and $\tau 7.5$ for the protons on the allylic and benzylic methylene units, a two proton singlet at $\tau 3.2$ for the aromatic protons in addition to the signal for the three vinylic protons between $\tau 3.8$ and $\tau 5.2$.

Treatment of the olefinic pyridine CXXVII with excess diborane followed by oxidation of the intermediate organoborane with alkaline hydrogen peroxide gave a high yield of the primary alcohol CXXVIII which solidified after distillation. The mass spectrum of the alcohol had a parent peak at m/e 179 and a base peak at m/e 134



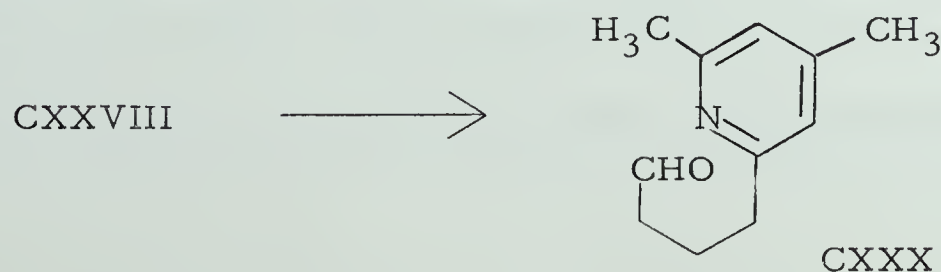
which is attributed to an ion with the structure CXXIX.



In addition to bands due to the aromatic portion of the molecule at 1600 and 1560 cm^{-1} , the infrared spectrum of the alcohol showed hydroxyl absorption at 3610 (sharp) and 3400 (broad) cm^{-1} .

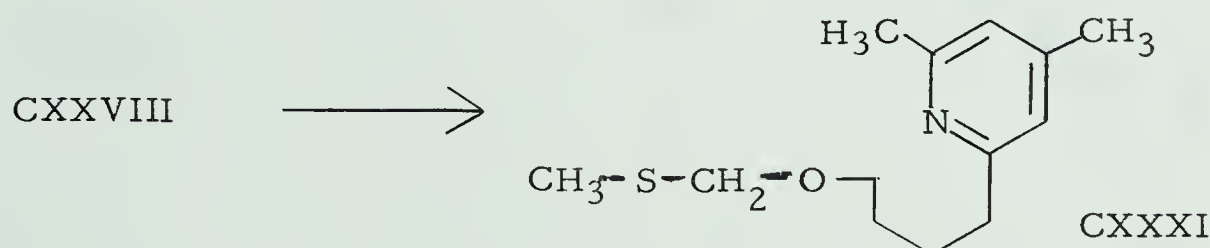
The N.M.R. spectrum of the alcohol CXXVIII contained three proton singlets at τ 7.75 and τ 7.52 due to the protons on the aromatic C-methyl groups, a two proton triplet at τ 6.32 for the protons on the methylene unit carrying the hydroxyl group and a two proton singlet at τ 3.22 for the protons bonded to the aromatic ring.

At this point we attempted to oxidize the primary alcohol CXXVIII to the corresponding aldehyde CXXX. The method of choice



for carrying out this transformation appeared to be the sulfoxide-carbodiimide oxidation method reported by Pfitzner and Moffat in 1965 (84). These workers have shown that when a primary alcohol is reacted with dimethylsulfoxide and dicyclohexylcarbodiimide in the presence of an acid catalyst, the corresponding aldehyde is usually obtained in good yield.

When, however, the alcohol CXXVIII was treated with dimethylsulfoxide and dicyclohexylcarbodiimide in the presence of anhydrous phosphoric acid none of the expected aldehyde CXXX was obtained. Indeed spectral characteristics of the crude product indicated that the methylthiomethyl ether CXXXI had formed.

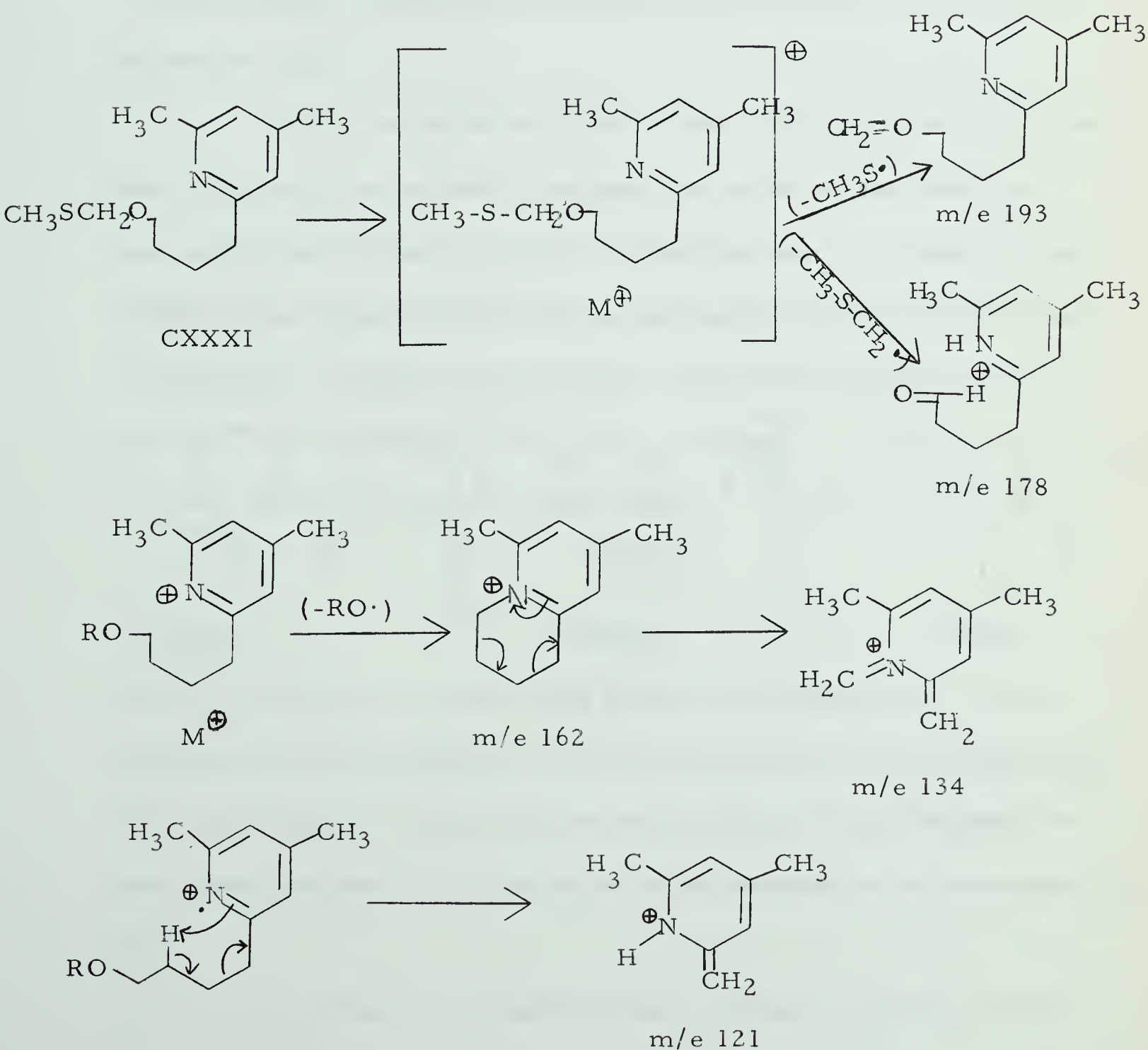


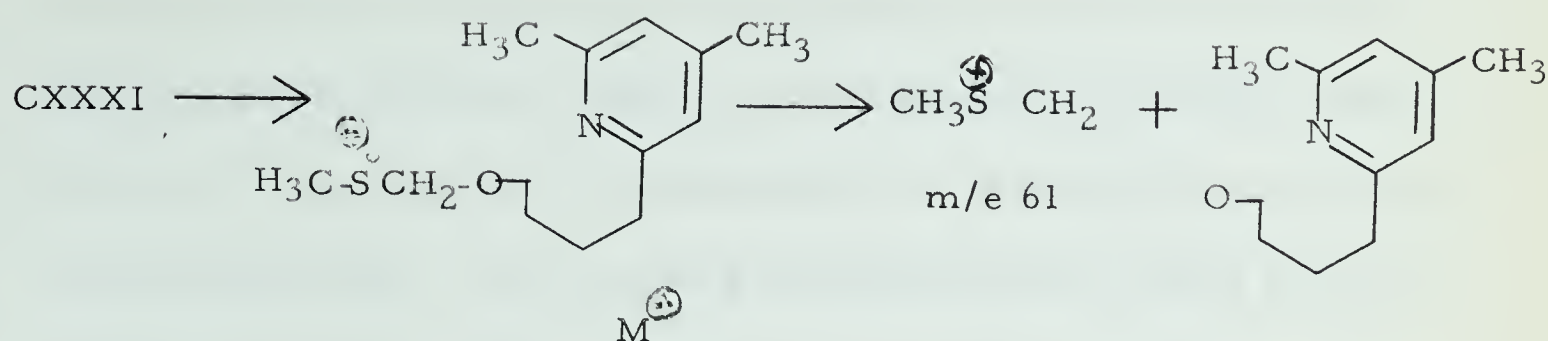
The infrared spectrum of the product had, in addition to bands at 1600 and 1560 cm^{-1} due to pyridine absorption, two strong bands at 1100 and 1070 cm^{-1} attributed to the stretching vibrations of the mixed acetal function.

In addition to signals at τ 7.75 and τ 7.50 for the aromatic C-methyl groups, the N.M.R. spectrum of CXXXI contained a sharp three proton singlet at τ 7.87 attributed to the protons on the methyl group attached to the sulfur atom and a sharp two proton singlet at τ 5.4

for the protons on the methylene unit between the sulfur and the oxygen atom.

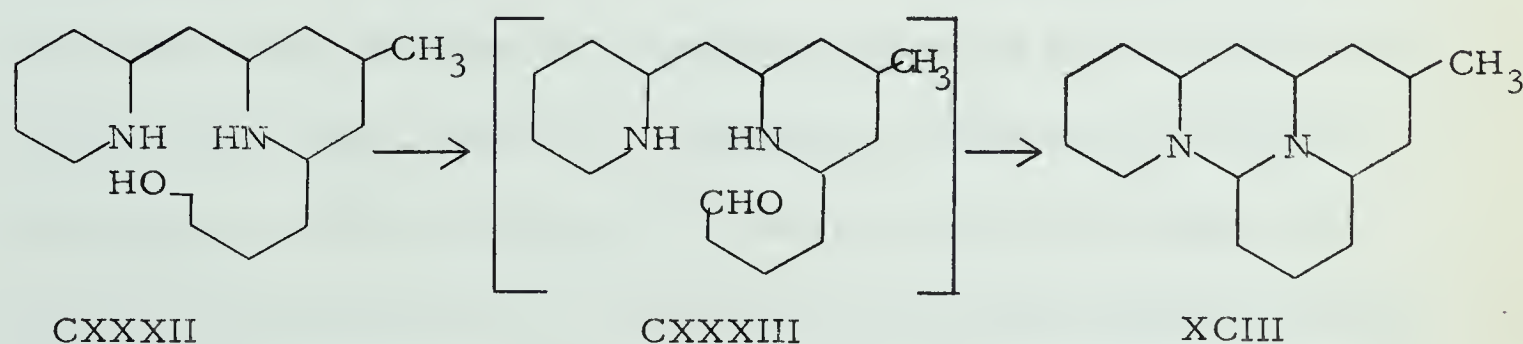
The mass spectrum confirmed that the methylthiomethyl ether CXXXI had formed since it contained a parent peak at m/e 239 with other significant peaks occurring at m/e 193, 178, 162, 134, 121 and 61 attributed to ions which may be formed by the schemes shown below.





The formation of methylthiomethyl ethers as by-products in the sulfoxide-carbodiimide oxidation procedure has been observed before (84, 87).

Since the oxidation of the alcohol CXXVIII did not yield the desired product we decided to postpone the oxidation step until the last step in the synthesis since if we could prepare the dibasic alcohol CXXXII, then oxidation should yield the aldehyde CXXXIII which would be expected to condense spontaneously with the two nitrogen atoms to

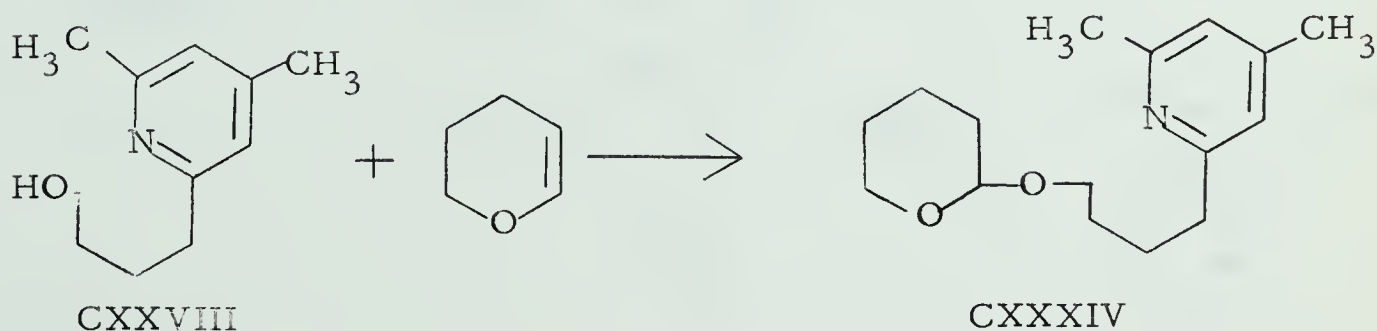


yield the tetracyclic ceruine ring skeleton XCIII directly. If the condensation of the aldehyde with the amine system occurs immediately after the formation of the aldehyde, this sequence also eliminates the worrisome problem of over oxidation of the aldehyde to the corresponding acid.

In order to proceed with the synthesis using the pyridine

alcohol CXXVIII it was necessary to protect the hydroxyl group with a blocking group which was stable to strong bases, in particular phenyllithium. The utility of 2,3-dihydropyran for blocking hydroxyl groups is well known (85). The resulting tetrahydropyranyl ethers are very stable to alkali and anionic reagents but are easily hydrolyzed by treatment with dilute mineral acid.

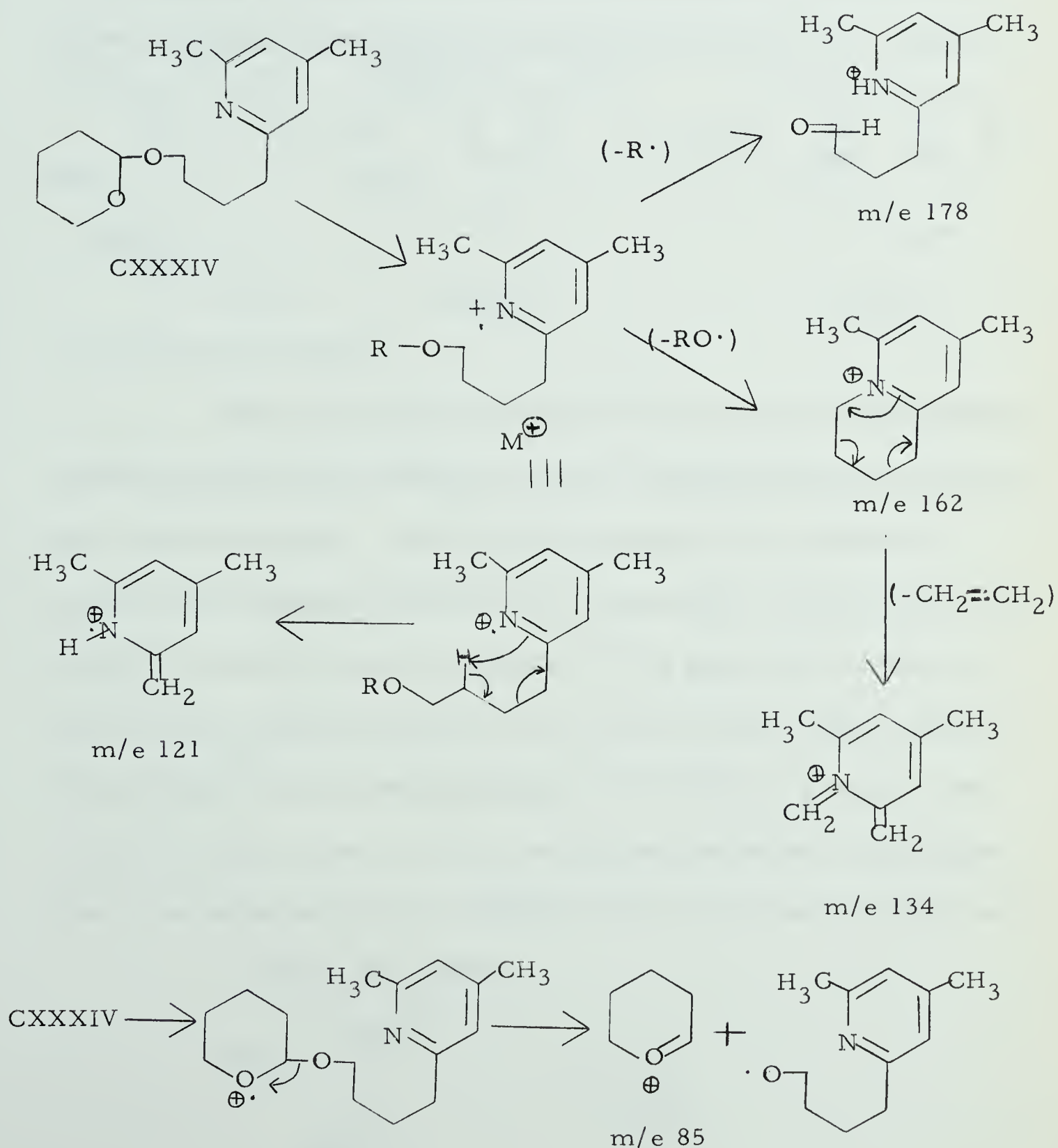
When the pyridine alcohol CXXVIII was reacted with dihydropyran in the presence of an acid catalyst a high yield of the pyridine acetal CXXXIV was obtained. The fact that the mixed acetal CXXXIV



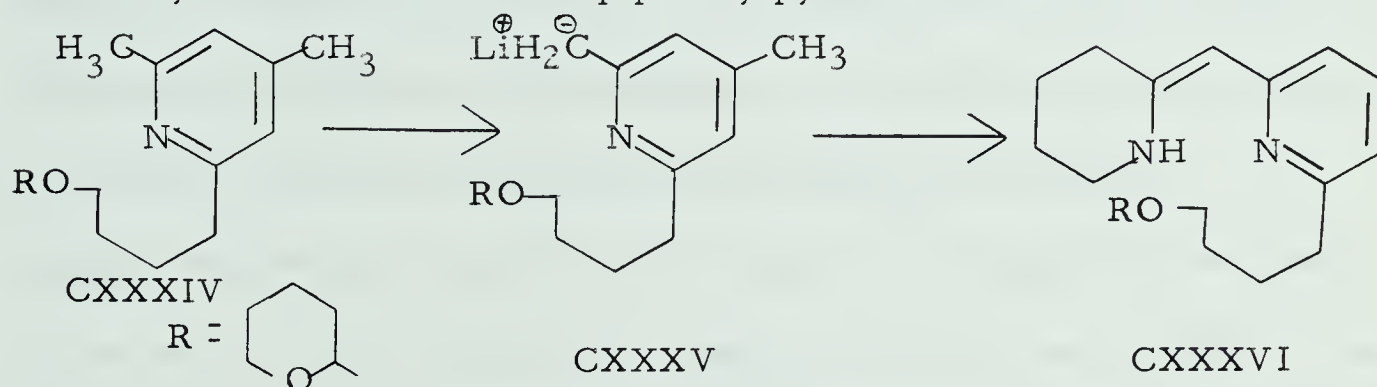
had formed was indicated by the infrared spectrum which no longer had hydroxyl absorption and which, in addition to bands due to pyridine absorption at 1600 and 1560 cm^{-1} , now had a series of strong bands between 1020 and 1140 cm^{-1} attributed to the carbon-oxygen stretching vibrations of the mixed acetal system.

The N.M.R. spectrum of the pyridine acetal CXXXIV contained the expected signals due to the aromatic methyl protons at τ 7.75 and τ 7.52 and also had a one proton signal as a broad singlet at τ 5.4 attributed to the proton on the carbon between the two oxygen atoms.

The mass spectrum confirmed that the pyridine acetal CXXXIV had formed. It revealed a weak molecular ion peak at m/e 263 and in addition to peaks at m/e 178, 162, 134, and 121 it had a peak at m/e 85 attributed to an ion from the tetrahydropyranyl portion of the molecule as shown below.

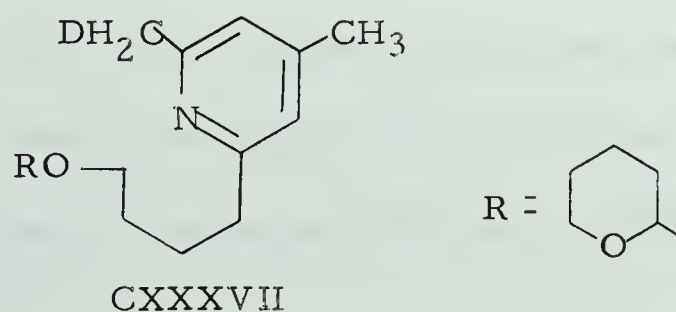


We were now ready to attempt the condensation of the lithium salt of the pyridine acetal CXXXIV with the iminoester CIV. It was expected that reaction of the pyridine acetal CXXXIV with one equivalent of phenyllithium would lead to the formation of the monolithium salt CXXXV which on condensation with the iminoester of valerolactam should yield the unsaturated piperidylpyridine CXXXVI as a mixture



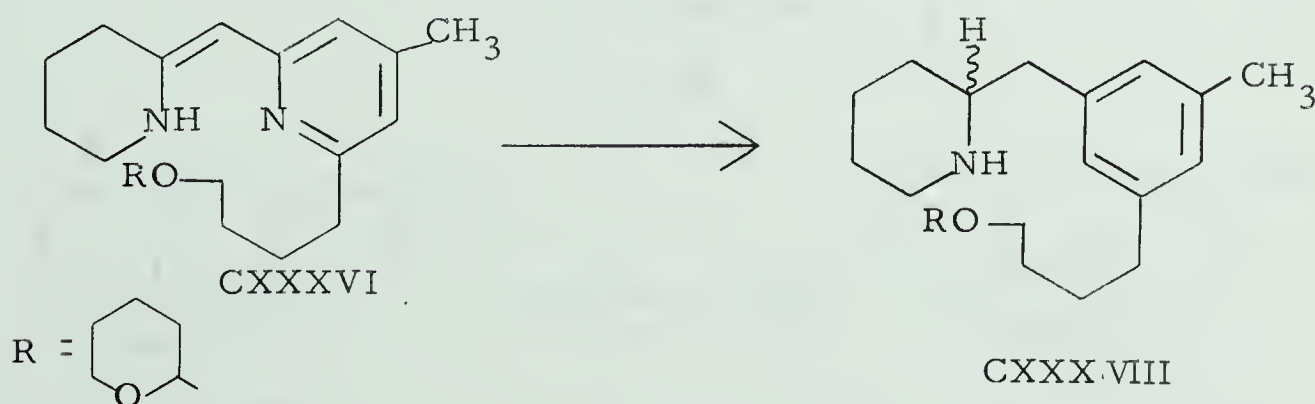
of double bond isomers.

When the pyridine acetal CXXXIV was reacted with phenyllithium an aliquot was removed from the reaction mixture and plunged into deuterium oxide. The N.M.R. spectrum of the product so obtained was identical with the N.M.R. spectrum of the pyridine acetal CXXXIV except that now the signal at $\tau 7.52$ integrated for just over two protons instead of three as in that of the pyridine acetal CXXXIV. This indicates that the desired lithium salt CXXXV is present in the reaction mixture since on work-up with deuterium oxide it should give the mono-deuteroderivative CXXXVII which should now show only two



protons on the methyl group alpha to the nitrogen atom in the N.M.R. spectrum.

When the lithium salt CXXXV was condensed with the imino-ester of valerolactam there resulted, after removal of low boiling components by distillation approximately a one to one mixture of the starting pyridine acetal CXXXIV and a slightly more polar product as indicated by thin layer chromatography. This more polar product presumably was the unsaturated piperidylpyridine CXXXVI. No attempt was made to separate this mixture as it quickly turned dark brown in color indicating that possibly the product was unstable. Instead the crude mixture of the pyridine acetal CXXXIV and the unsaturated compound CXXXVI was subjected immediately to catalytic hydrogenation over palladium-charcoal at atmospheric pressure in order to reduce the exocyclic double bond in CXXXVI and form the piperidylpyridine

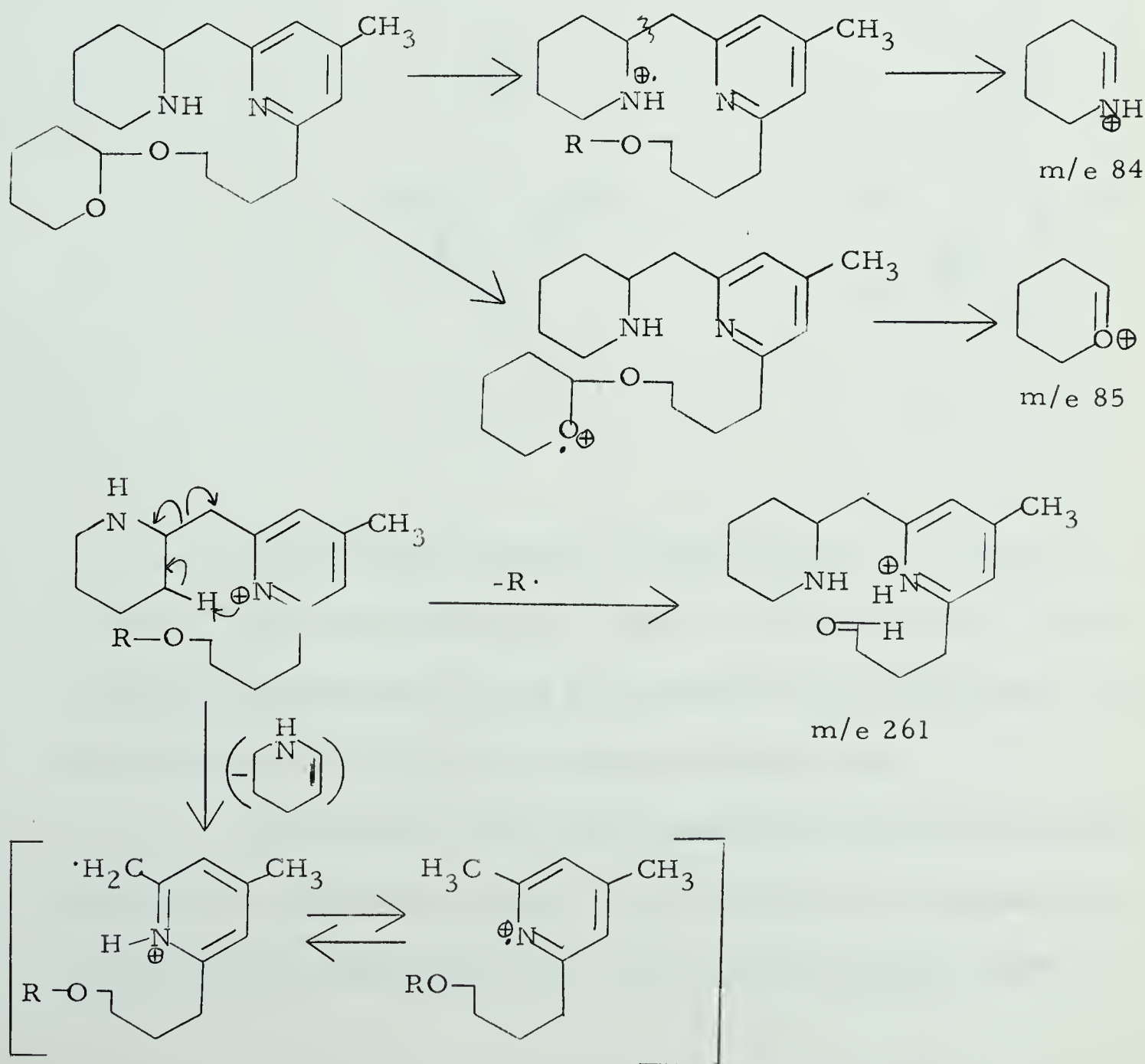


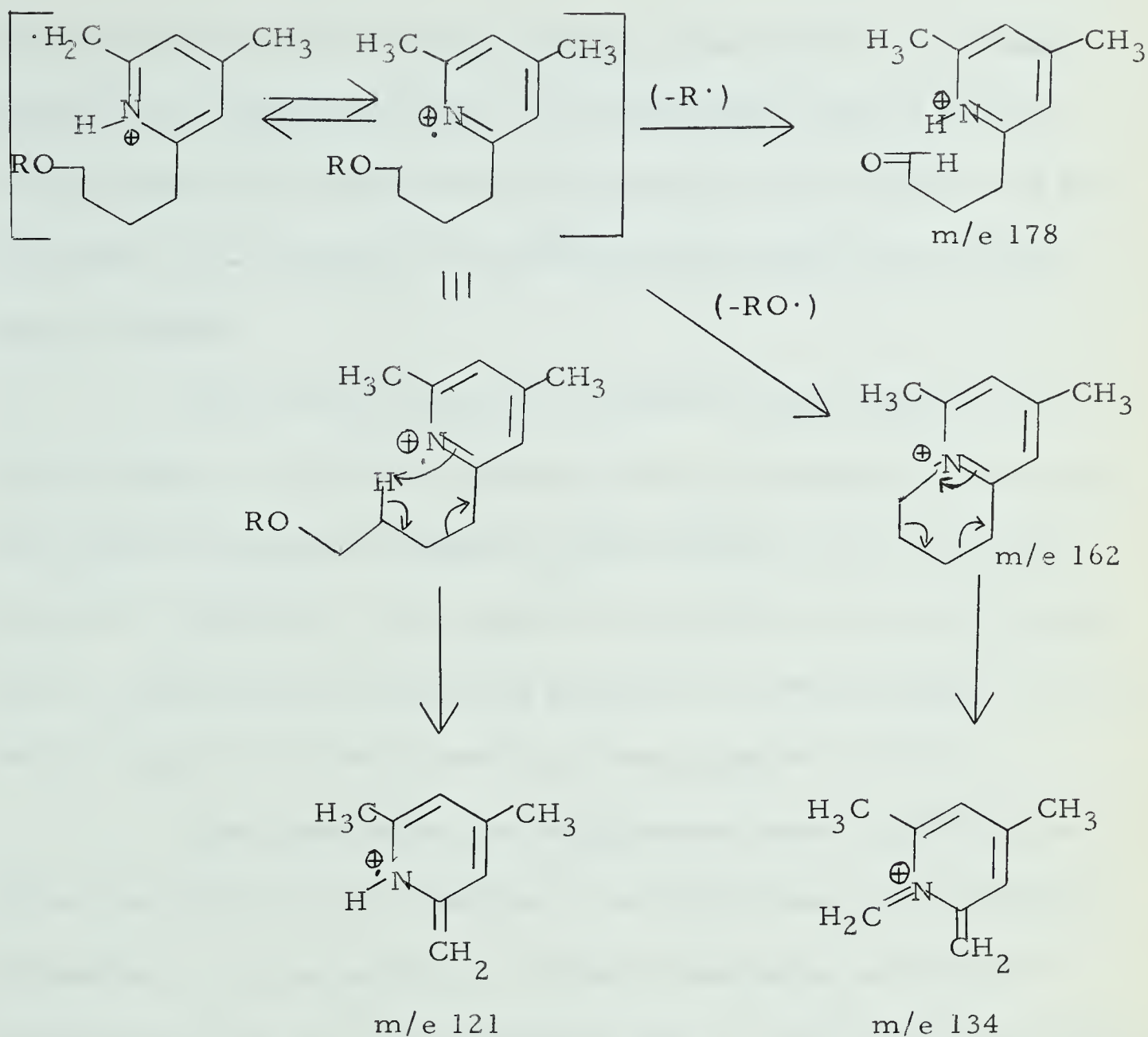
acetal CXXXVIII.

The crude reaction mixture obtained from catalytic hydrogenation again showed two major spots on thin layer chromatography, one having the same R_f as the pyridine acetal CXXXIV, the other considerably

more polar than the pyridine acetal. Separation of the two components by column chromatography gave the starting pyridine acetal CXXXIV and an equal amount of the desired piperidylpyridine acetal CXXXVIII.

The mass spectrum of the piperidylpyridine acetal CXXXVIII did not show a parent peak but did show strong peaks at m/e 84 and m/e 85 confirming the presence of a piperidine ring and a tetrahydropyran ring. Other significant peaks appeared at m/e 261, 178, 162, 134 and 121. A possible fragmentation scheme follows.





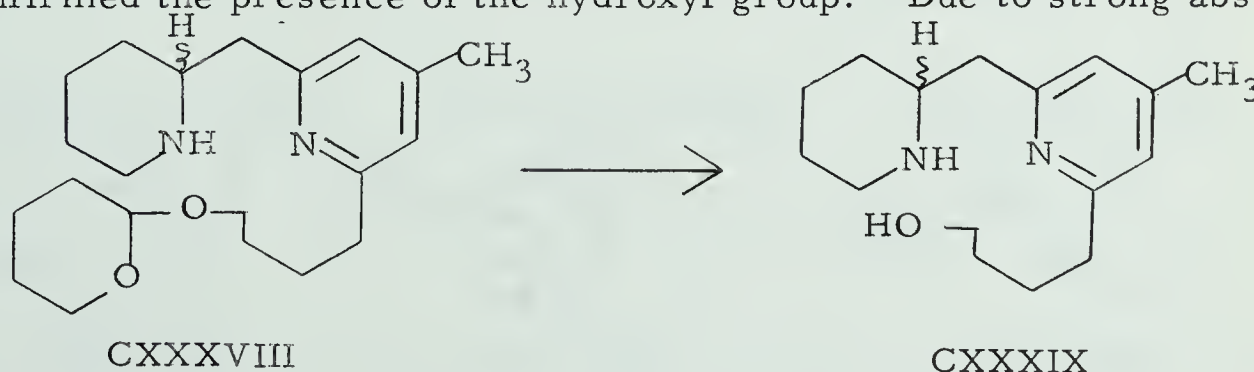
The infrared spectrum of CXXXVIII revealed a band at 3300 cm^{-1} due to N-H absorption, bands at 1600 and 1560 cm^{-1} due to pyridine absorption and several strong bands between 1020 and 1140 cm^{-1} due to absorption by the acetal portion of the molecule.

As expected, the N.M.R. spectrum of CXXXVIII indicated the presence of only one aromatic C-methyl group which appeared as a three proton singlet at τ 7.72. The fact that the methyl signal

which appeared at τ 7.52 in the pyridine acetal CXXXIV is no longer present in the piperidylpyridine acetal CXXXVIII confirms that the condensation of the lithium salt of the pyridine acetal CXXXIV with the iminoester CIV took place on the methyl group alpha to the nitrogen atom in CXXXIV.

The N.M.R. spectrum of CXXXVIII also contained a one proton singlet at τ 7.55 which disappeared on exchange with deuterium oxide and thus has been assigned as the signal due to the N-H proton present in CXXXVIII. The signal for the proton on the carbon between the two oxygen atoms in CXXXVIII appeared as a broad singlet at τ 5.42 and the signal for the two aromatic protons appeared at τ 3.2.

Hydrolysis of the piperidylpyridine acetal CXXXVIII with dilute hydrochloric acid yielded the piperidylpyridine alcohol CXXXIX isolated as a viscous yellow oil. Infrared absorption at 3610 cm^{-1} confirmed the presence of the hydroxyl group. Due to strong absorption

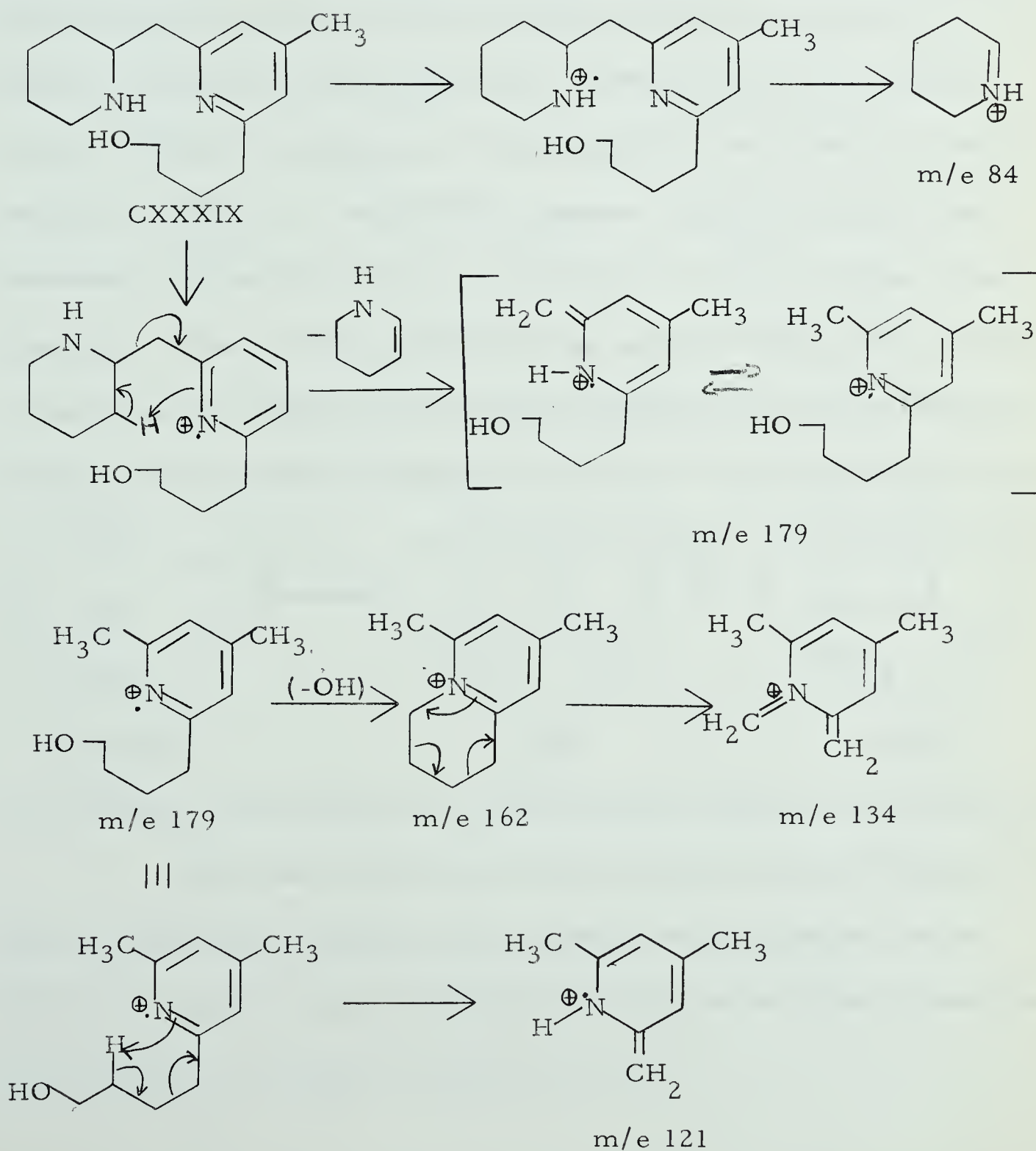


between 3500 and 3100 cm^{-1} the absorption band due to the N-H function could not be distinguished. The alcohol CXXXIX also showed bands at 1605 and 1550 cm^{-1} due to the pyridine ring.

In addition to other signals, the N.M.R. spectrum of the

alcohol CXXXIX contained a three proton singlet at τ 7.7 (aromatic C-methyl), a two proton triplet at τ 6.4 ($\text{CH}_2\text{-CH}_2\text{-OH}$) and a two proton singlet at τ 3.2 (aromatic protons).

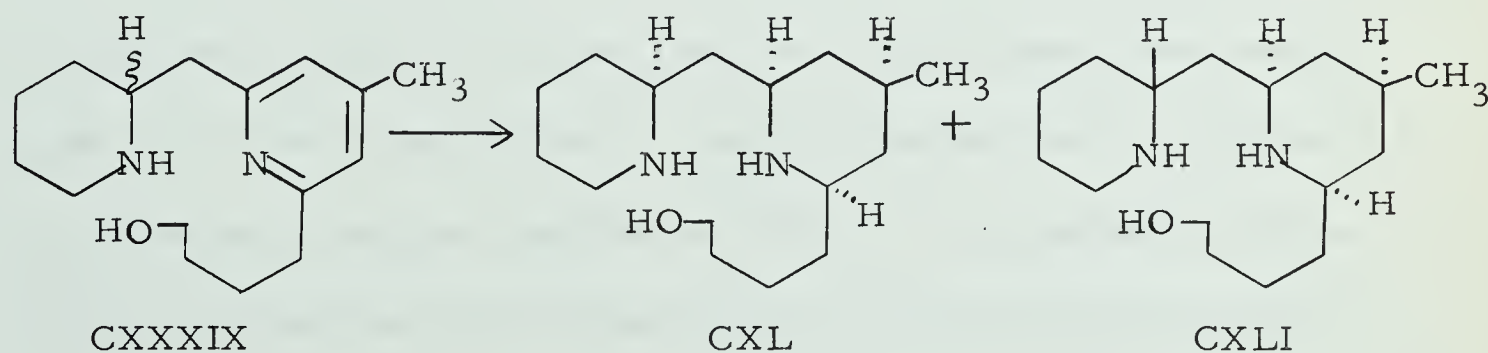
The mass spectrum of the alcohol CXXXIX had a very weak parent peak at m/e 262 with other major peaks occurring at m/e 179, 134, 121 (base peak) and 84.



Acetylation of the piperidylpyridine alcohol CXXXIX

converted it to a non-crystalline derivative which showed both acetate ($1740, 1240 \text{ cm}^{-1}$) and acetamide (1650 cm^{-1}) absorption in the infrared spectrum confirming the presence of both a hydroxyl and a secondary amino function in CXXXIX.

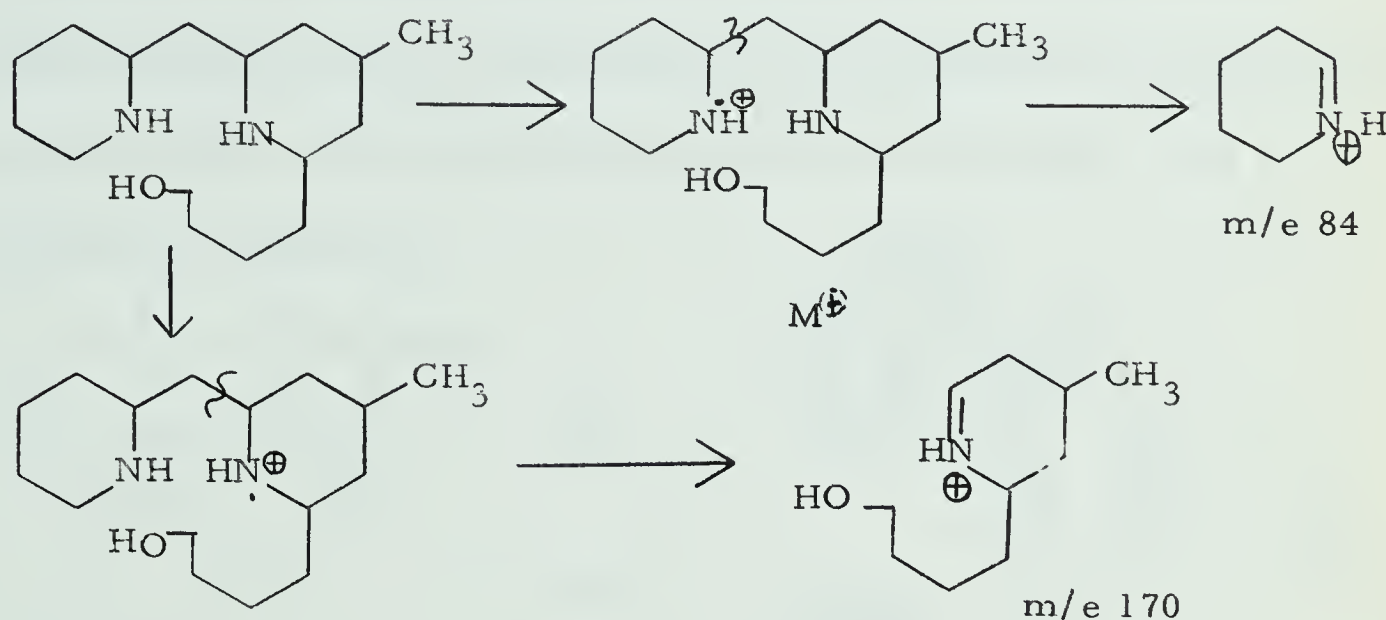
Catalytic hydrogenation of the piperidylpyridine alcohol CXXXIX under a variety of mild conditions failed to bring about the desired reduction of the pyridine ring. However when the pyridine alcohol CXXXIX was subjected to hydrogenation over rhodium-charcoal catalyst at 2000 p.s.i. and 100°C a mixture consisting mainly of two products, CXL and CXLI (only one enantiomer of each is shown), was produced. The fact that we had the fully saturated dipiperidine alcohols in hand was indicated by the infrared spectrum of the mixture which no longer showed pyridine absorption at 1600 cm^{-1} but did show the presence



of a hydroxyl group (3610 cm^{-1}) and a secondary amino function (3250 cm^{-1}).

The N.M.R. spectrum of the mixture of dipiperidine alcohols CXL and CXLI had doublets for two different methyl groups, one at $\tau 9.05$ ($J=6$ cps) the other at $\tau 8.85$ ($J=6$ cps) and no longer showed low field signals for aromatic or olefinic protons.

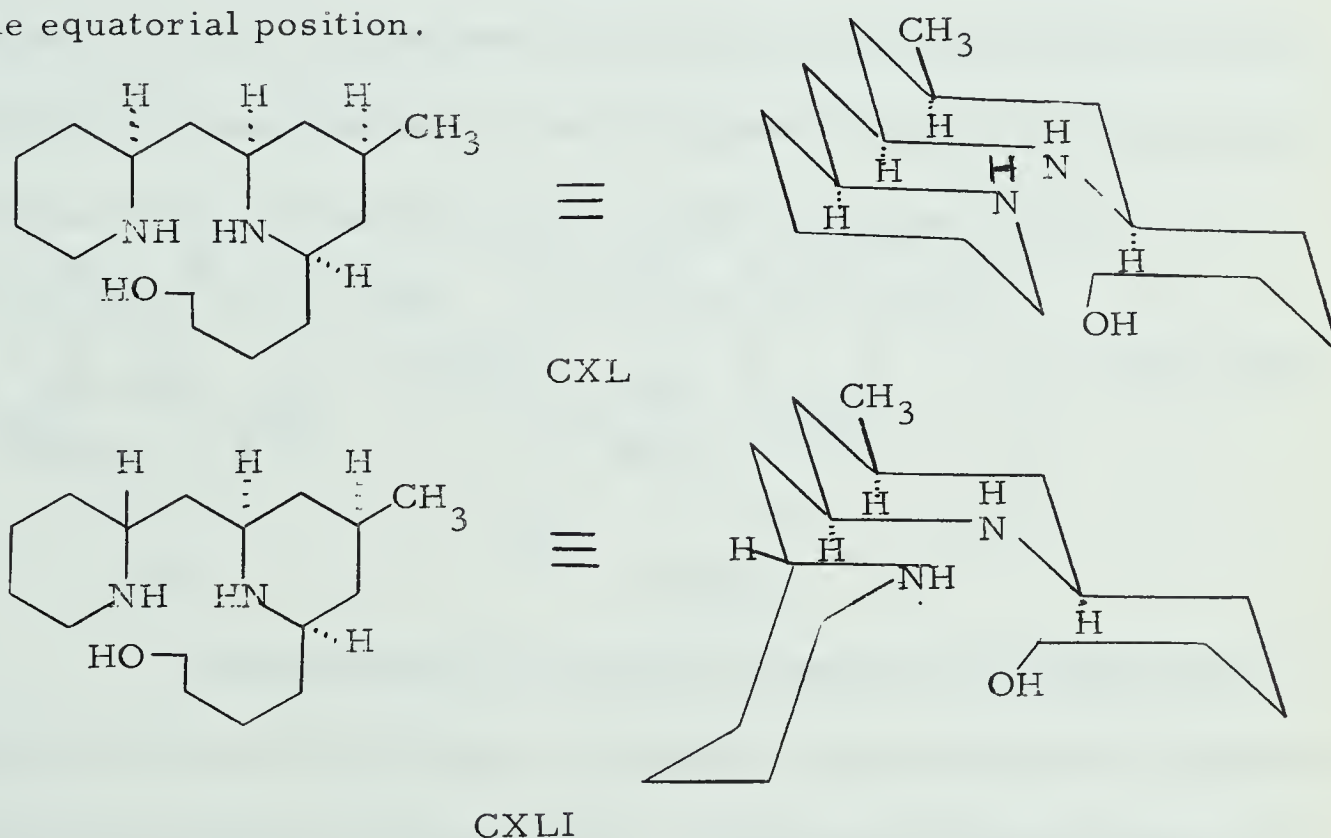
The mass spectrum of the mixture confirmed that the saturated compounds had been obtained since it had a parent peak at m/e 268 and now contained two major peaks at m/e 170 (67%) and m/e 84 (100%) which can readily be formed from the molecular ion as shown below.



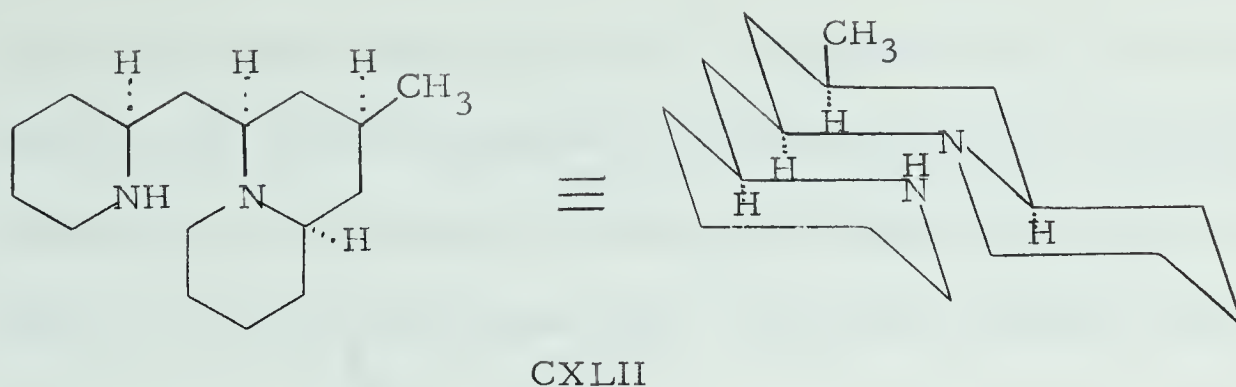
Acetylation of the mixture of dipiperidine alcohols with acetic anhydride-pyridine transformed it to a viscous oil which showed infrared absorption at 1735 and 1240 cm^{-1} ($-OAc$) and a very intense band at 1635 cm^{-1} (acetamide). The fact that the band at 1635 cm^{-1} was much more intense than that at 1735 cm^{-1} is consistent with the presence of one O-acetyl function and two N-acetyl functions in the molecule.

On the assumption that catalytic hydrogenation of the pyridine ring in CXXXIX results in overall cis-addition of hydrogen (86), we propose the stereochemistry of the two reduced compounds to be that shown in CXL and CXLI. This stereochemical assignment was

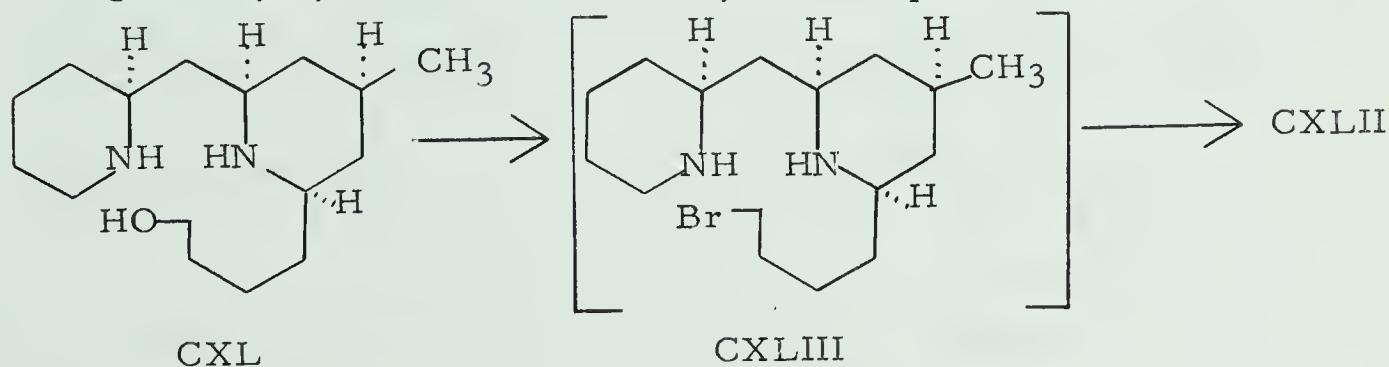
confirmed when it was found that chemical reduction, which presumably yields the thermodynamically most stable product, of the pyridine ring in CXXXIX with sodium in isoamyl alcohol gave the same mixture of products as was obtained from catalytic reduction of CXXXIX. The thermodynamically most stable reduction products should have the stereochemistry shown in CXL and CXLI since with this stereochemistry all three bulky substituents on the trisubstituted piperidine ring are in the equatorial position.



Having obtained the mixture of dipiperidine alcohols CXL and CXLI, we were now ready to complete the final steps in the synthesis of the ceruine ring skeleton. At this time a tricyclic compound CXLII with the proposed stereochemistry as shown (see later) had been prepared in these laboratories from the natural series of compounds by S. Valverde-Lopez. We now set about to attempt to correlate our



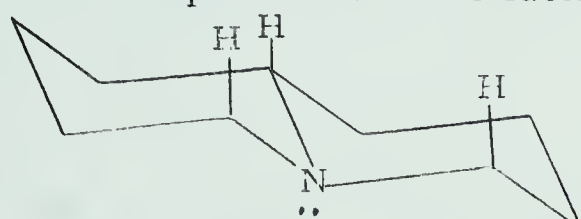
synthetic series with the natural series by preparing the tricyclic compound CXLII. It was hoped that treatment of the dipiperidine alcohol CXL with concentrated hydrobromic acid would transform the alcohol to the intermediate bromo compound CXLIII which should then undergo ready cyclization to the tricyclic compound CXLII.



When preliminary attempts to separate the dipiperidine alcohols CXL and CXLI failed, the mixture was subjected to treatment with boiling 48% hydrobromic acid. The product obtained from this reaction was composed of two major components which showed very similar R_f values on thin layer chromatography.

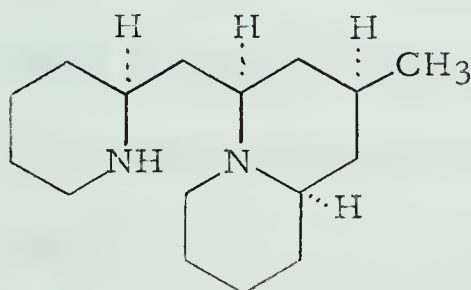
The infrared spectrum of the mixture of products no longer contained hydroxyl absorption but did show N-H absorption at 3280 cm^{-1} as well as "Bohlmann bands" at 2800 , 2740 and 2620 cm^{-1} . Bohlmann (88) has shown that the presence of the system CXLIV with at least two

carbon-hydrogen bonds orientated 1,2-transdiaxially to the unshared electron pair of the nitrogen atom, may be detected in a quinolizidine molecule by the appearance of three to six bands in the region 2900-2600 cm^{-1} of its infrared spectrum. The lack of hydroxyl absorption

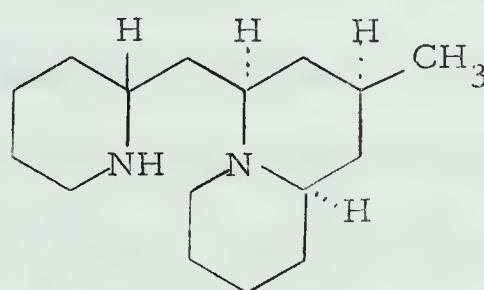


CXLIV

and the presence of "Bohlmann bands" in the infrared spectrum indicated that we had in hand the mixture of tricyclic compounds CXLII and CXLV derived from the dipiperidine alcohols CXL and CXLI, respectively.

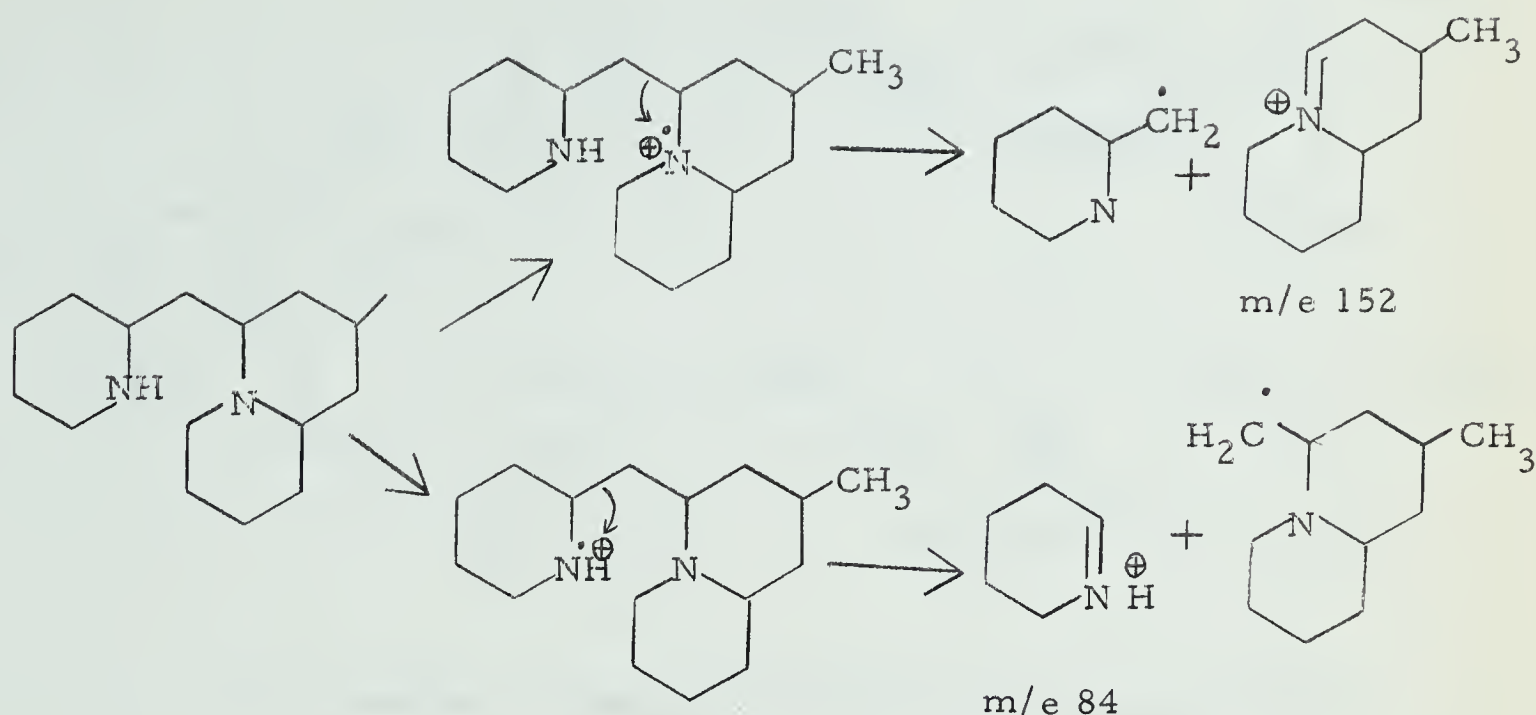


CXLII



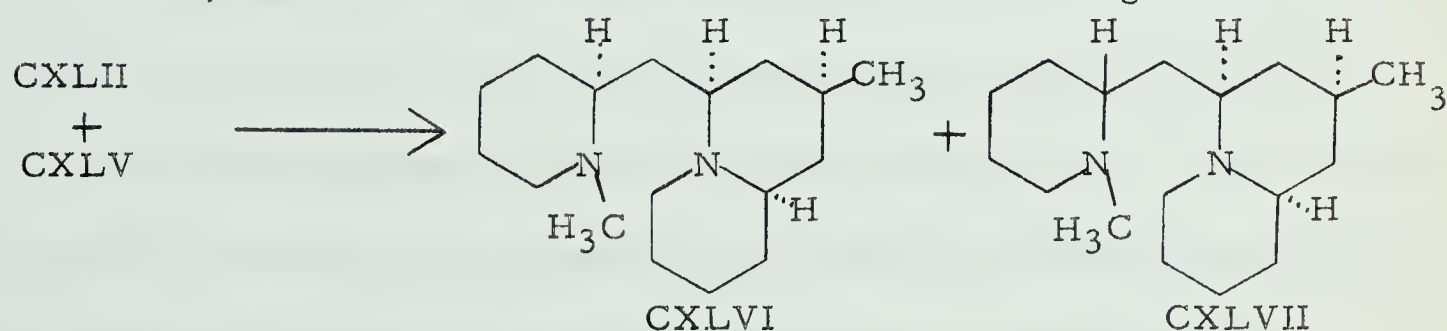
CXLV

The mass spectrum of the mixture of tricyclic compounds CXLII and CXLV, which showed a parent peak at m/e 250 and contained only two other prominent peaks, one at m/e 152 and one at m/e 84, was virtually identical with that of the tricyclic N-H compound obtained from the natural series. The fact that the mass spectra of the synthetic mixture and the natural derivative were so similar was the first indication that we had indeed obtained a correlation between the synthetic and the natural series.

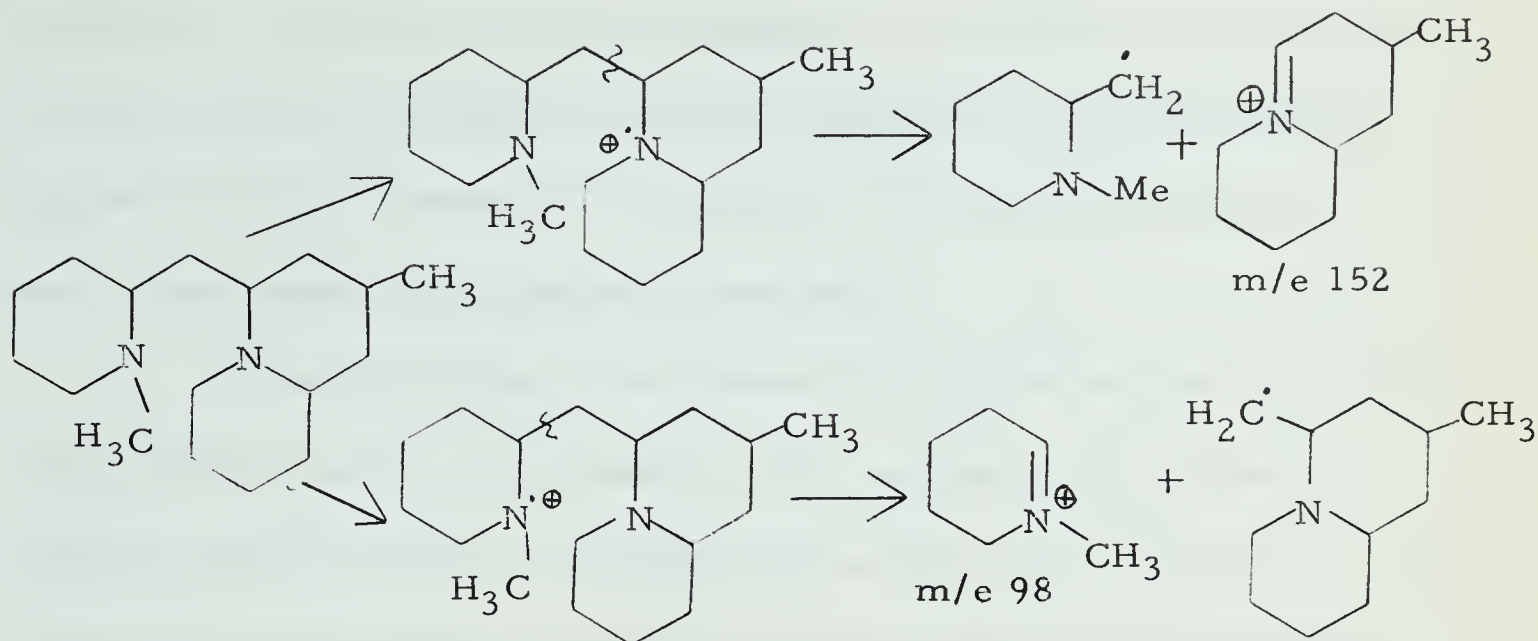


Methylation of the mixture of tricyclic N-H compounds

CXLII and CXLV with formic acid-formaldehyde (89) gave the mixture of N-methyl derivatives CXLVI and CXLVII which no longer showed



N-H absorption in the infrared spectrum but did show "Bohlmann bands" at 2780, 2710 and 2610 cm^{-1} . The mass spectrum of the mixture of N-methyl compounds CXLVI and CXLVII had a parent peak at m/e 264 and had large peaks at m/e 152 and m/e 98 attributed to the ions shown below. The mass spectrum of the synthetic mixture again was virtually identical with that of the authentic N-methyl derivative prepared from the tricyclic N-H compound obtained from the natural series.

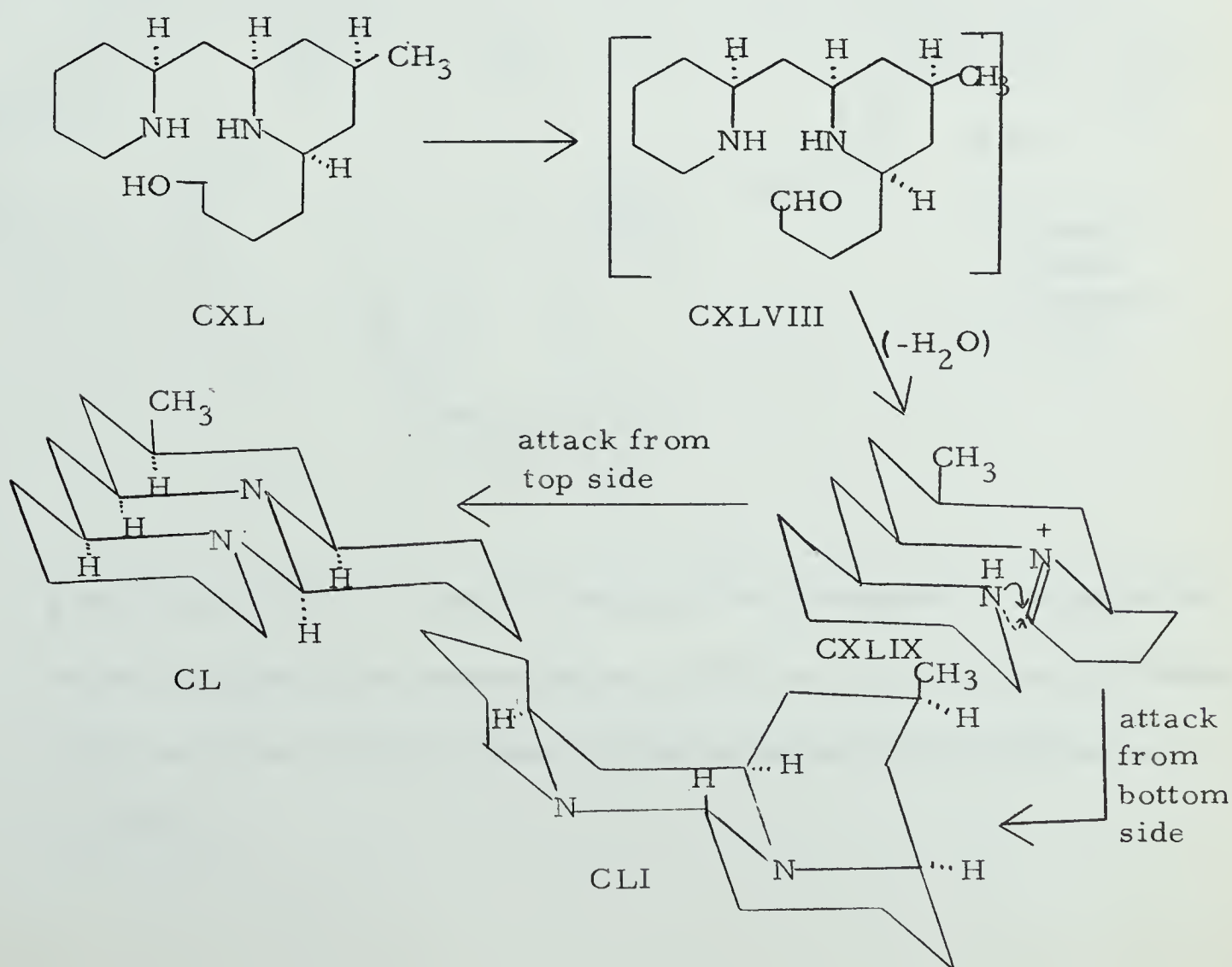


The mixture of synthetic tricyclic N-H compounds CXLII and CXLV was separated by gas-liquid chromatography. In this way a synthetic tricyclic N-H compound was obtained which was identical (retention time on gas-liquid chromatography, infrared spectrum in carbon tetrachloride, thin layer chromatographic behavior) with the tricyclic N-H compound obtained from the natural series. The second synthetic tricyclic N-H compound had a shorter retention time than did the other and its infrared spectrum was different from that of the authentic tricyclic N-H compound.

Presumably the synthetic tricyclic N-H compound which was identical with the authentic tricyclic compound has the stereochemistry shown in CXLII but it must be pointed out that the fact that we had obtained a synthetic compound which was identical with the authentic tricyclic compound does not prove the stereochemistry of the authentic compound since we were not able at this point to distinguish the stereo-

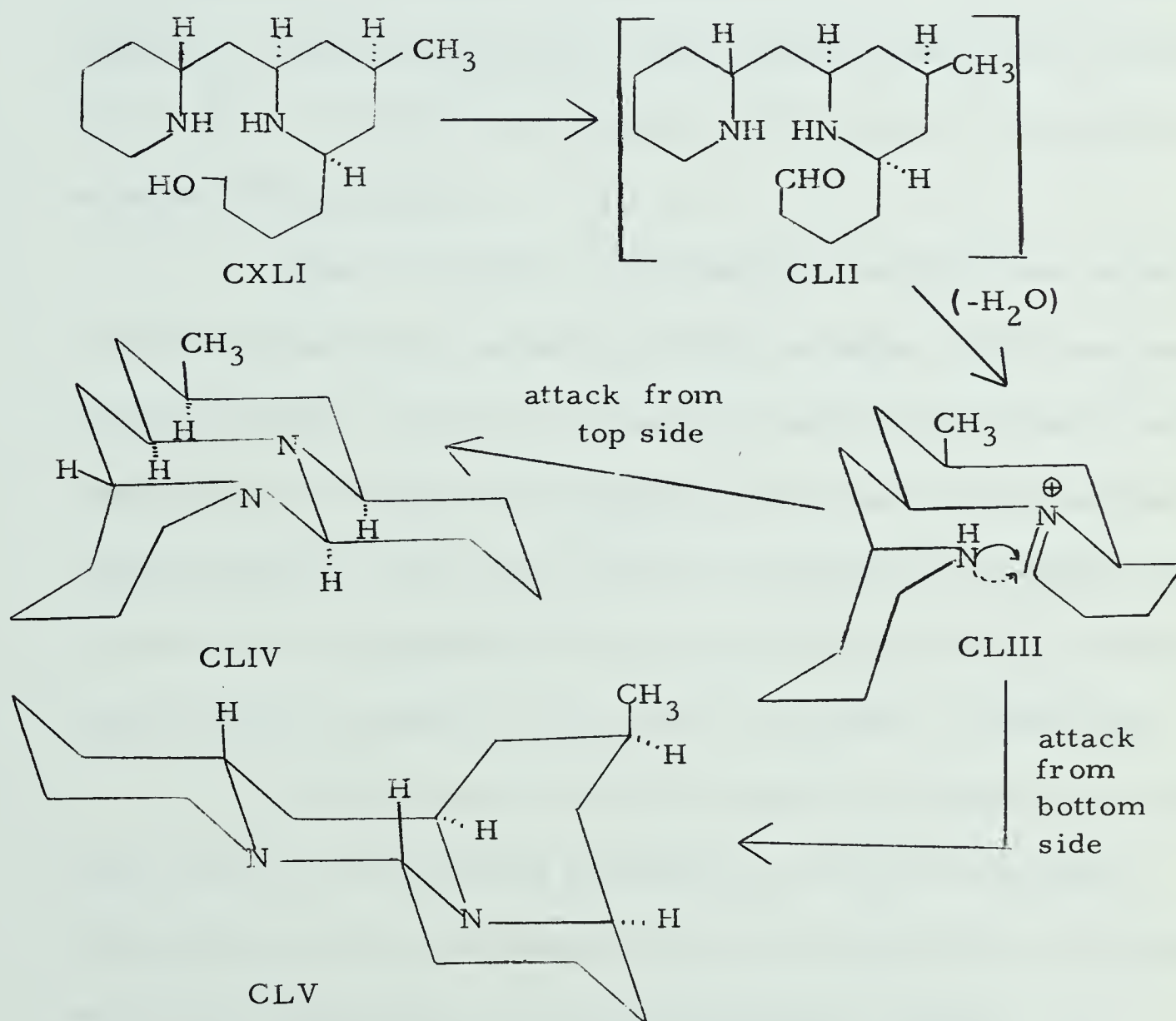
chemistry of the two synthetic compounds. It suffices to say that the fact that one of the synthetic tricyclic compounds is identical with the authentic tricyclic compound is consistent with the stereochemical assignment made for the authentic compound.

Having obtained a correlation between the synthetic and the natural series we were now ready to try to prepare the ceruine ring skeleton from the mixture of dipiperidine alcohols CXL and CXLI. In theory four stereochemically different tetracyclic compounds could be obtained from the mixture of the two dipiperidine alcohols CXL and CXLI. Oxidation of CXL would give the aldehyde CXLVIII which on ring closure via the intermediate immonium ion CXLIX could give either CL, the result of attack of the secondary nitrogen atom from the



top side of the immonium ion CXLIX, or CLI, the result of attack of the secondary nitrogen atom from the bottom side of the immonium ion CXLIX.

Oxidation of the dipiperdine alcohol CXLII would give the aldehyde CLII which on ring closure via the immonium ion CLIII could



give either CLIV, the result of attack of the secondary nitrogen atom on the top side of the immonium ion CLIII, or CLV, the result of attack of the secondary nitrogen atom on the bottom side of the immonium ion CLIII.

Examination of molecular models however, led us to believe that, whereas both CLIV and CLV could be readily formed from the ion CLIII, the formation of the all cis tetracyclic system CL (which contains two trans quinolizidine systems) from the ion CXLIX would be highly favored over the formation of CLI, which contains two cis quinolizidine systems. Hence we expected to obtain only three tetracyclic compounds CL, CLIV and CLV from the reaction of the mixture of dipiperidine alcohols CXL and CXLI.

When the mixture of alcohols CXL and CXLI was oxidized with dimethylsulfoxide-carbodiimide (84), or better, with chromium trioxide-pyridine, a mixture of products resulted which showed only two spots on thin layer chromatography, both much less polar than the starting alcohols. The same mixture of products was obtained, though in lower yield, by oxidation of the mixture of alcohols CXL and CXLI with chromium trioxide in acetic acid or with Jones' reagent (90).

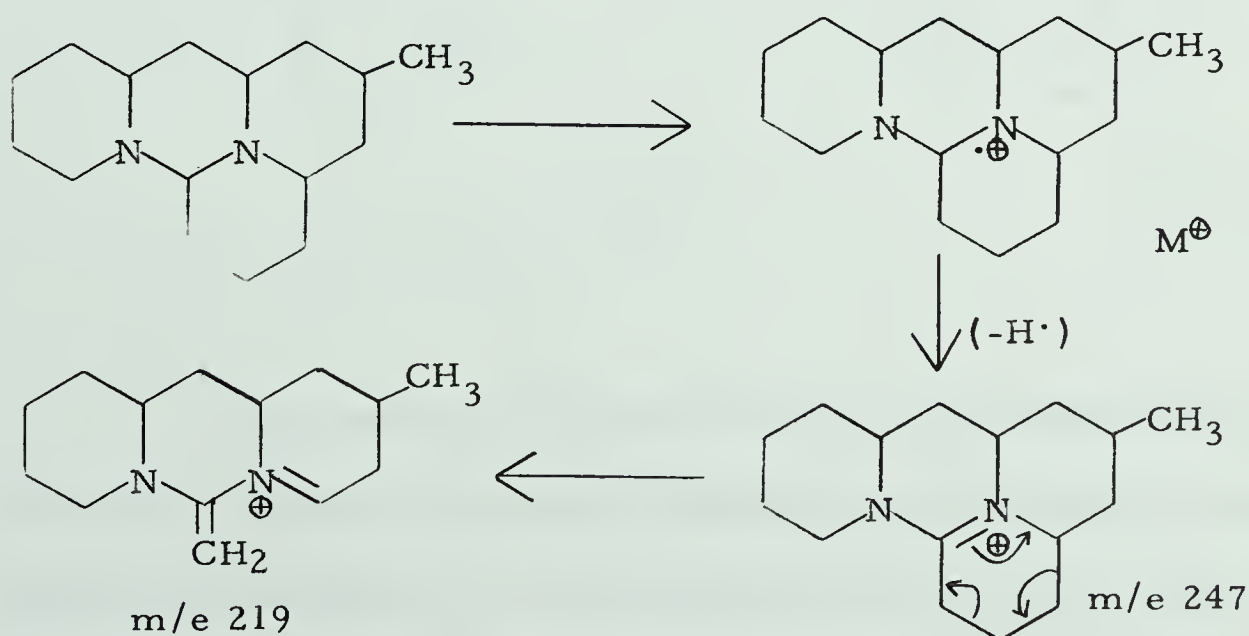
The mass spectrum of the mixture of products contained a parent peak at m/e 248 and a base peak at m/e 219 as did that of dihydrodeoxycernuine, indicating that probably the mixture of compounds was in fact composed of the desired tetracyclic products.

Column chromatography of the mixture of synthetic tetracyclic products cleanly separated the materials accounting for the two spots. The faster running material was obtained as a colorless solid and was found to be identical (infrared spectrum in carbon tetrachloride,

mass spectrum, thin layer chromatographic behavior) with dihydrodeoxyepialloceruine obtained from the natural series by S. Valverde-Lopez.

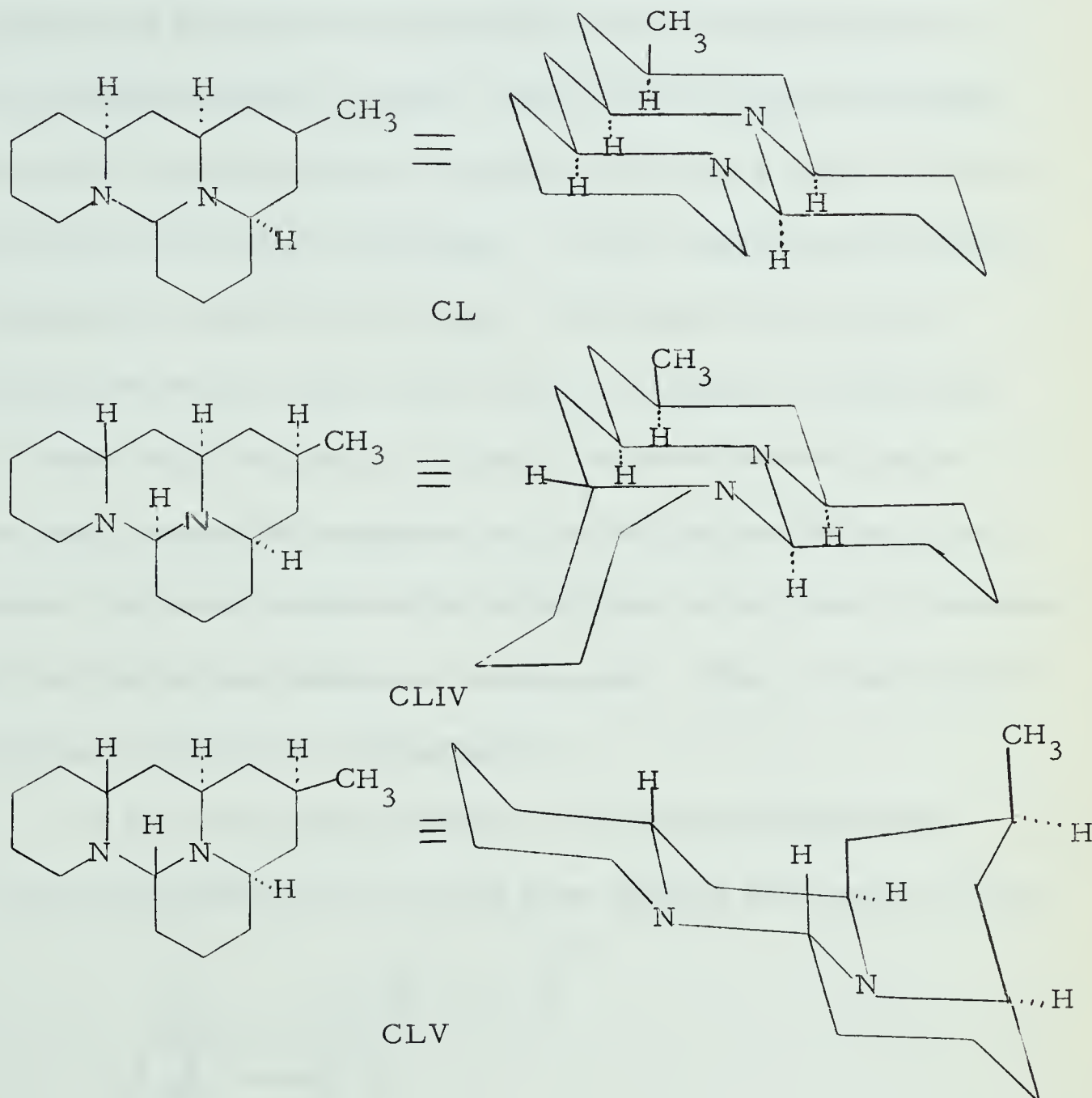
The slower running component was obtained as a colorless oil which did not solidify but which still showed only one spot on thin layer chromatography. However our suspicions that this oil was in fact a mixture of epimeric tetracyclic compounds was confirmed by its N.M.R. spectrum which showed signals for two different secondary C-methyl groups, one at τ 9.16 ($J=5.5$ cps), the other at τ 9.07 ($J=6$ cps).

The mass spectra of both the solid tetracyclic compound and the oily mixture of tetracyclic compounds had parent peaks at m/e 248 and base peaks at m/e 219 (see below). The mass spectra of the solid and the oil were virtually identical with one another and were very similar to the mass spectrum of dihydrodeoxyceruine.



Satisfied that we had indeed prepared the ceruine ring skeleton we now attempted to elucidate the stereochemistry of the

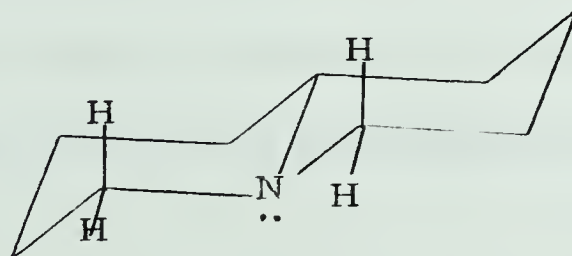
synthetic tetracyclic compounds. As was discussed before we felt that we had obtained the three tetracyclic compounds CL, CLIV and CLV.



For reasons to be discussed later, the solid synthetic tetracyclic compound which was identical with dehydrodeoxyepiallocer nuine was assigned the stereochemistry shown by CL. The two synthetic tetracyclic compounds forming the mixture were believed to be CLIV and CLV.

Examination of the structures CL, CLIV and CLV reveals that in CL both nitrogen atoms have three hydrogens on alpha carbon atoms which are orientated transdiaxially to the unshared electron pair on nitrogen whereas, in either CLIV or CLV, only one nitrogen atom has three hydrogen atoms on alpha carbon atoms which are transdiaxial to the electron pair on nitrogen. Hence, qualitatively at least, the compound CL should show stronger "Bohlmann bands" in the infrared spectrum than either CLIV, CLV or a mixture of CLIV and CLV. When infrared spectra of equal concentration were run on both the solid tetracyclic compound and the oily mixture of tetracyclic compounds, the solid compound did indeed show more intense "Bohlmann bands" than did the oily mixture of compounds. This is in agreement with structure CL for the solid compound.

It has been shown (91) that, in the quinolizidine system CLVI, the axial protons on the carbon atom alpha to the nitrogen appear



CLVI

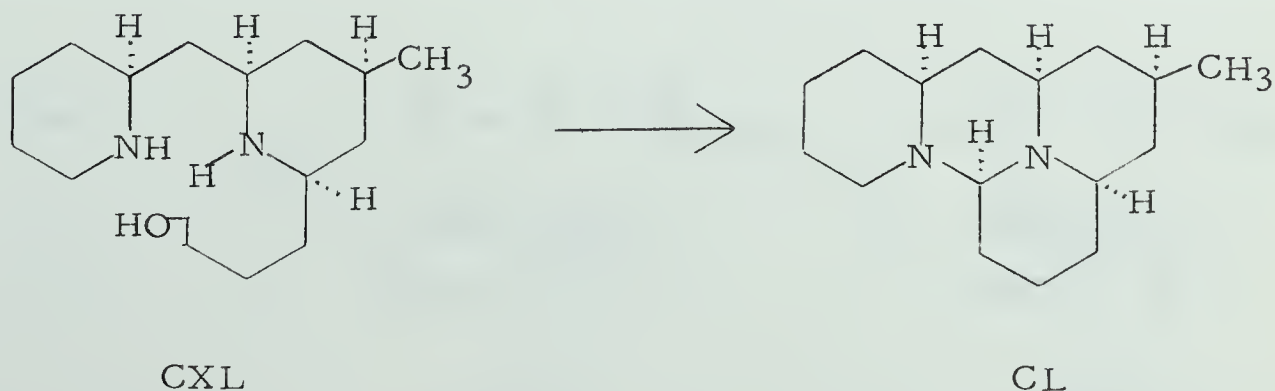
at about 0.8 to 0.9 p.p.m. to higher field than do the equatorial protons in the N.M.R. spectrum. The equatorial protons usually appear in the approximate range τ 7.0-7.7.

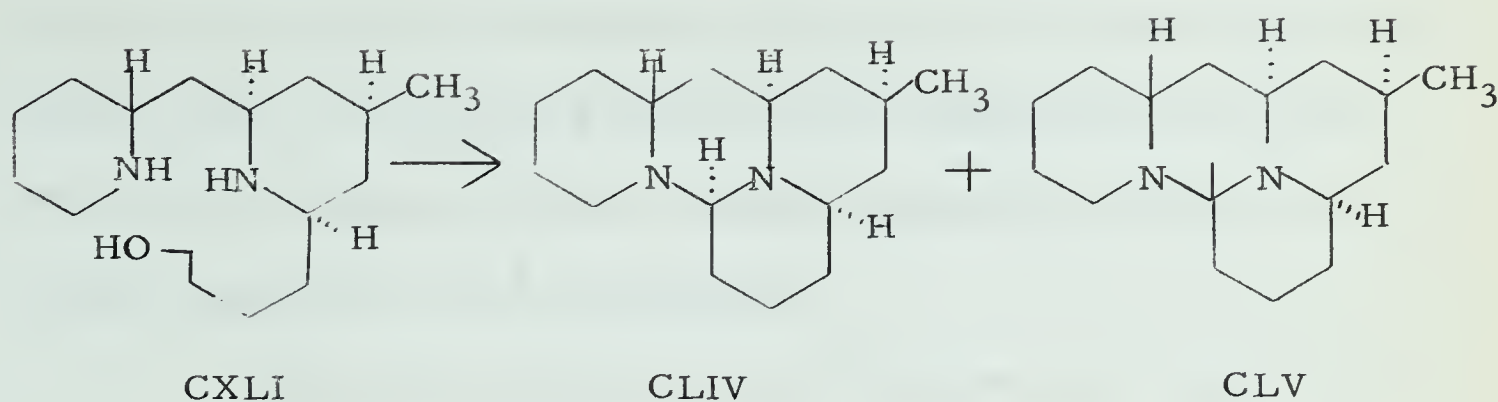
When the N.M.R. spectrum of the synthetic dihydrodeoxy-

epiallocernuine was examined, signals for only two protons appeared below τ 7.8, in agreement with structure CL for the product. The broad doublet ($J=9$ cps) which appeared at τ 6.83 was assigned to the axial proton on the carbon atom between the two nitrogen atoms in CL, whereas the one proton multiplet ($W_{1/2} \approx 15$ cps) which appeared at τ 7.65 was attributed to the single equatorial proton on the carbons alpha to nitrogen present in CL. Both CLIV and CLV would be expected to show signals for more than two low field (below τ 7.8) protons. Indeed the N.M.R. spectrum of the oily mixture of tetracyclic compounds was complex in the region τ 6.5 to τ 7.8 and indicated the presence of several protons absorbing in this region.

On the basis of the above spectral evidence we felt confident that dihydrodeoxyepiallocernuine had the stereochemistry shown in CL, whereas the oily mixture of synthetic products was composed of a mixture of CLIV and CLV.

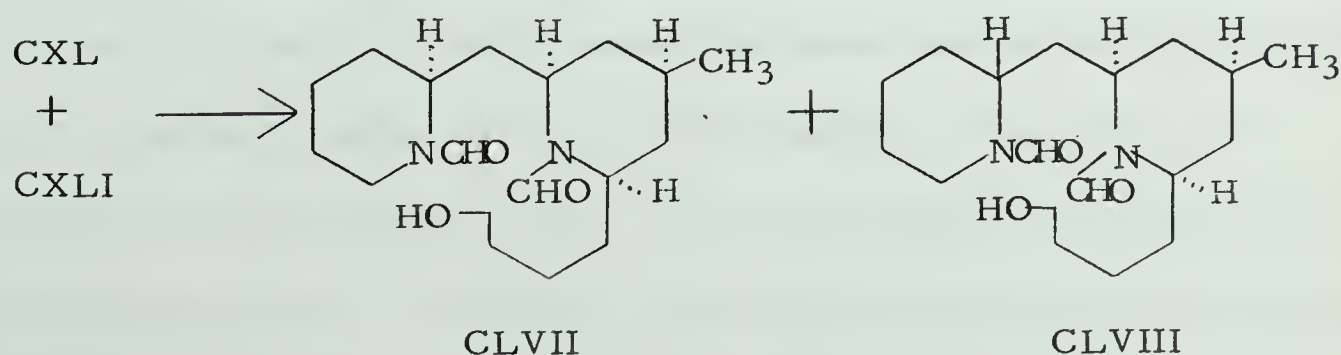
In order to confirm the assignment made, it was necessary to separate the mixture of dipiperidine alcohols CXL and CXLI. If the





mixture of alcohols CXL and CXLI could be separated, then oxidation of one of them should give only dihydrodeoxyepiallocerbuine CL, whereas oxidation of the other should give the mixture of tetracyclic compounds CLIV and CLV. If, of course, oxidation of one of the alcohols gave a mixture of dihydrodeoxyepiallocerbuine and another tetracyclic compound then dihydrodeoxyepiallocerbuine must have either structure CLIV or CLV, and, as a result, the stereochemical argument made for dihydrodeoxyepiallocerbuine (see above) would be wrong.

Formylation (67) of the mixture of dipiperidine alcohols CXL and CXLI gave, after hydrolysis of the O-formate esters in aqueous potassium carbonate solution, the mixture of neutral di-N-formylpiperidines CLVII and CLVIII. The mixture showed two distinct



spots on thin layer chromatography although the difference in R_f values was not large. The mixture of di-N-formyl compounds had infrared absorption at 3620 and 3450 cm^{-1} (broad) (hydroxyl) in addition to an intense band at 1675 cm^{-1} (formamide).

The mixture of di-N-formyl compounds was separated by careful column chromatography. The faster running di-N-formyl compound, which shall be referred to as N-formyl A, was obtained as an oil which showed infrared absorption at 3620 and 3400 (broad) cm^{-1} (hydroxyl) and at 1675 cm^{-1} (formamide).

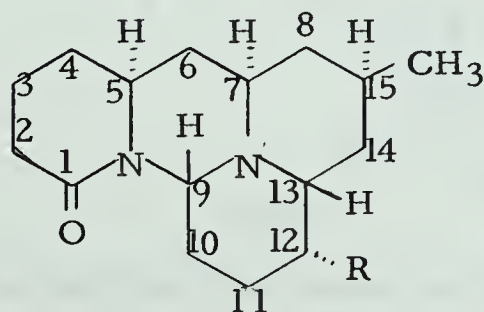
Hydrolysis of N-formyl A in refluxing 5% sulfuric acid gave the less polar of the two dipiperidine alcohols which on oxidation with chromium trioxide-pyridine gave a single product, identical (infrared spectrum in carbon tetrachloride, thin layer chromatographic behavior) with the previously obtained dihydrodeoxyepiallocernuine. The fact that oxidation of the single alcohol gave only one tetracyclic product, dihydrodeoxyepiallocernuine, is consistent with structure CL for dihydrodeoxyepiallocernuine, structure CXL for the dipiperidine alcohol and structure CLVII for N-formyl A.

The more polar di-N-formyl compound (N-formyl B) was also obtained as an oil which showed infrared maxima at 3620 and 3450 cm^{-1} (hydroxyl) and at 1675 cm^{-1} (formamide). Hydrolysis of N-formyl B gave the more polar of the two dipiperidine alcohols as a colorless semisolid. Oxidation of the dipiperidine alcohol thus obtained

with chromium trioxide-pyridine gave an oily product which again showed only one spot on thin layer chromatography. However, the N.M.R. spectrum of this oil again indicated the presence of two components in that it displayed signals for two different secondary C-methyl groups (τ 9.16 and τ 9.07).

The fact that oxidation of the more polar dipiperidine alcohol results in the formation of two tetracyclic compounds is consistent with structures CLIV and CLV for the two tetracyclic products, structure CXLI for the more polar dipiperidine alcohol and structure CLVIII for N-formyl B.

Provided the stereochemical assignments made above are correct then this synthesis provides a proof of the relative stereochemistry of dihydrodeoxyepialloceraine (CL). It is now necessary to show how CL is formed in the natural series and also to show how the knowledge of its stereochemistry as derived here aids in settling the stereochemistry of ceraine (XI) and lycoceraine (XII). Ayer, Jenkins and Valverde-Lopez (93) suggested the stereochemistry shown in XI and XII on the basis of the following observations.

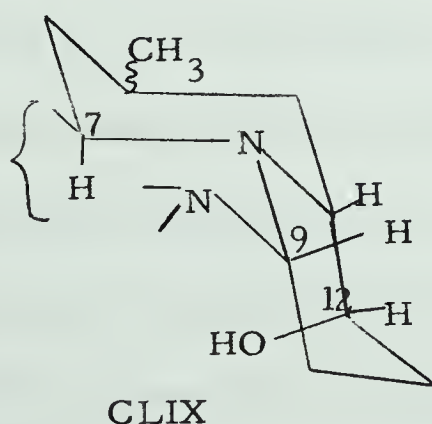


XI: R = H

XII: R = OH

N.M.R. measurements indicate that the hydroxyl group in lycocernuine is in the axial orientation since in O-acetyllycocernuine the proton at C-12 appears as a multiplet at τ 5.12 ($W_{1/2}$ 5 cps) indicative of an equatorial proton. Double irradiation experiments confirm this assignment since irradiation at τ 6.81 (C-13 proton) causes the signal at τ 5.12 to collapse to a triplet (J 2.5 cps) whereas irradiation at τ 8.12 (C-11 methylene) causes it to collapse to a doublet (J 2.1 cps).

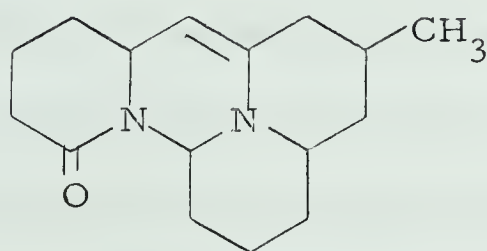
The fact that the axial hydroxyl group in lycocernuine (XII) is not hydrogen-bonded to the nitrogen suggests a cis-quinolizidine system in which the hydroxyl group is located in the ring to which the unshared electron pair on nitrogen bears an equatorial relationship (92). This leads to part structure CLIX (C-7 and C-9 not assigned) for lycocernuine. The lack of "Bohlmann bands" in the 2700 to 2800 cm^{-1} region of the infrared spectra of cernuine (XI) and lycocernuine (XII) is consistent with part structure CLIX.



The signal for the proton at C-9, which is deshielded by two nitrogen atoms, is clearly visible in the N.M.R. spectra of cernuine,

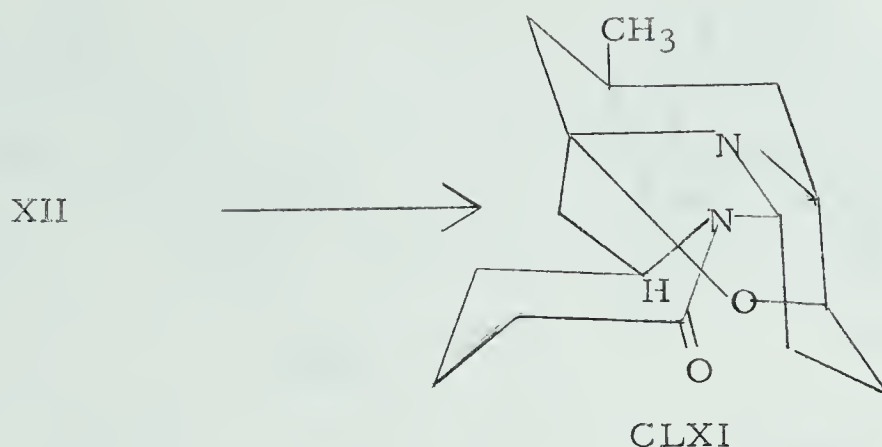
lycocernuine and many of their derivatives and appears as a quartet with one large splitting (10-12 cps) and one small splitting (2-4 cps), indicative of an axial hydrogen.

Mercuric acetate oxidation of both cernuine (XI) and lycocernuine (XII) occurs toward C-7, indicating a trans-diaxial relationship between the lone pair on the basic nitrogen and the C-7 hydrogen. Catalytic hydrogenation of the enamine CLX, obtained



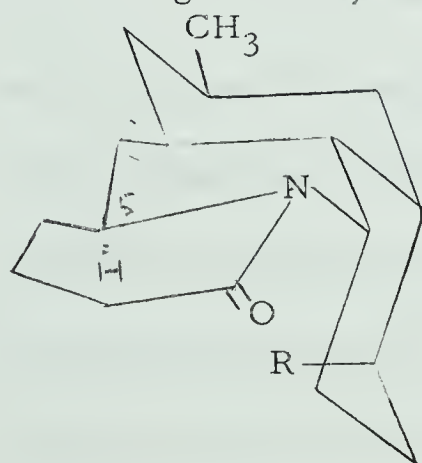
CLX

by mercuric acetate oxidation of cernuine (XI), gave cernuine (XI). The N.M.R. spectrum of the enamine CLX indicated the retention of the C-9 proton (quartet at τ 4.58) and showed a complex two proton signal at τ 5.8-6.0, attributed to the protons at C-5 and C-6. The chemical shift of the methine proton on C-15 was determined by spin decoupling of the methyl protons and shown to occur at τ 8.1 just as in cernuine. Hence the double bond in the enamine CLX cannot be in the 7, 8 or 13,14 position and since the $\Delta^{12(13)}$ olefin is the known anhydrolycocernuine which is not identical with the enamine CLX, the latter must be the $\Delta^{6(7)}$ isomer CLX. Mercuric acetate oxidation of lycocernuine (XII) gave the oxazolidine CLXI, which regenerates lycocernuine (XII) on catalytic hydrogenation.



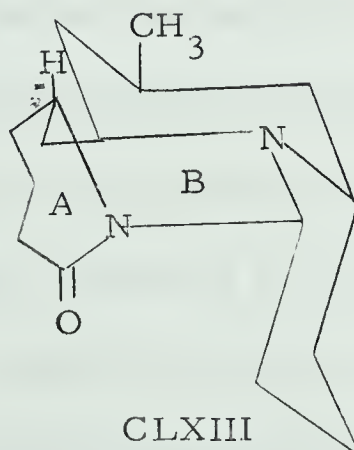
The stereochemistry at C-5 and C-15 was next assigned.

The two possibilities for cernuine at C-5 are shown in CLXII ($\equiv$ XI) and CLXIII. In CLXIII ring B is forced to adopt the boat conformation in order for the amide group to remain planar. Hydride reduction of cernuine gives dihydrodeoxycernuine which shows "Bohlmann bands"



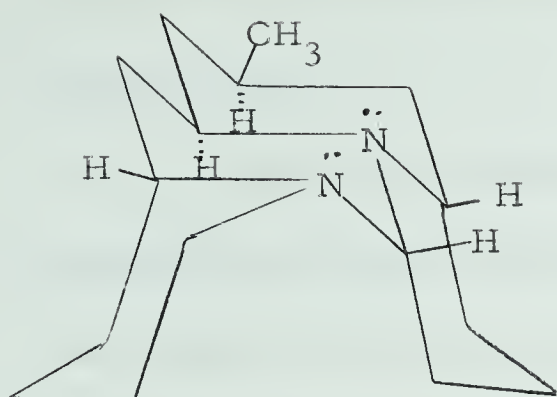
CLXII ($\equiv$ XI): R = H

CLXVI ($\equiv$ XII): R = OH

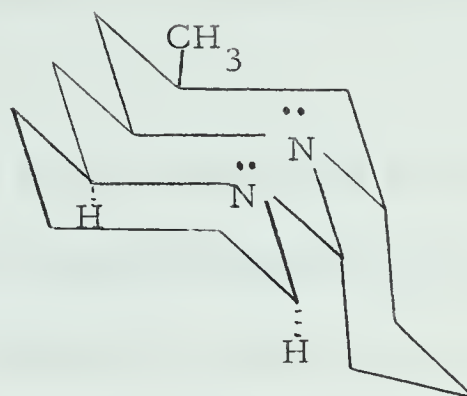


CLXIII

in the infrared spectrum. If CLXIII were the correct presentation of cernuine the product of hydride reduction would be expected to adopt the conformation shown in CLXIV which would not be expected to show "Bohlmann bands". The dihydrodeoxy compound from CLXII on the other hand would be expected to adopt the conformation shown in CLXV which would be expected to lead to "Bohlmann bands" in the infrared



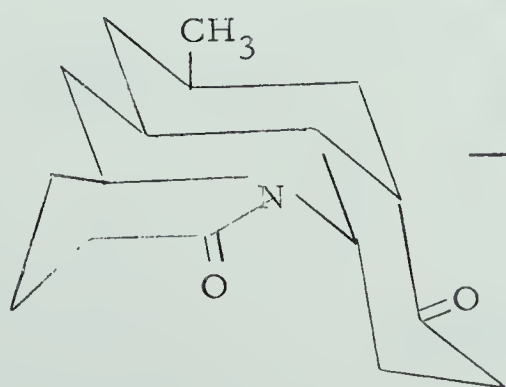
CLXIV



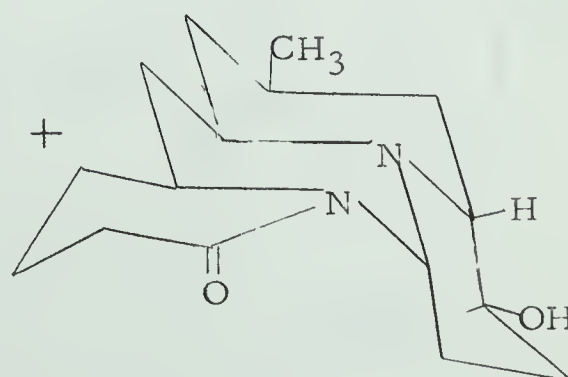
CLXV

spectrum. The appearance of "Bohlmann bands" in the infrared spectrum of dihydrodeoxycernuine is in agreement with the structure CLXII ($\equiv$ XI) for cernuine and structure CLXVI ($\equiv$ XII) for lycocernuine.

Though the stereochemistry of the C-15 methyl group was not rigorously assigned the equatorial configuration was favored since sodium borohydride reduction of dehydrolycocernuine CLXVII yields both lycocernuine CLXVI and the epimeric alcohol CLXVIII. If the methyl group at C-15 were axial, attack of the reducing agent from the backside to give the epimeric alcohol CLXVIII would be extremely hindered. Provided the stereochemical assignment made for the synthetic product is correct, the equatorial nature of the C-15 methyl



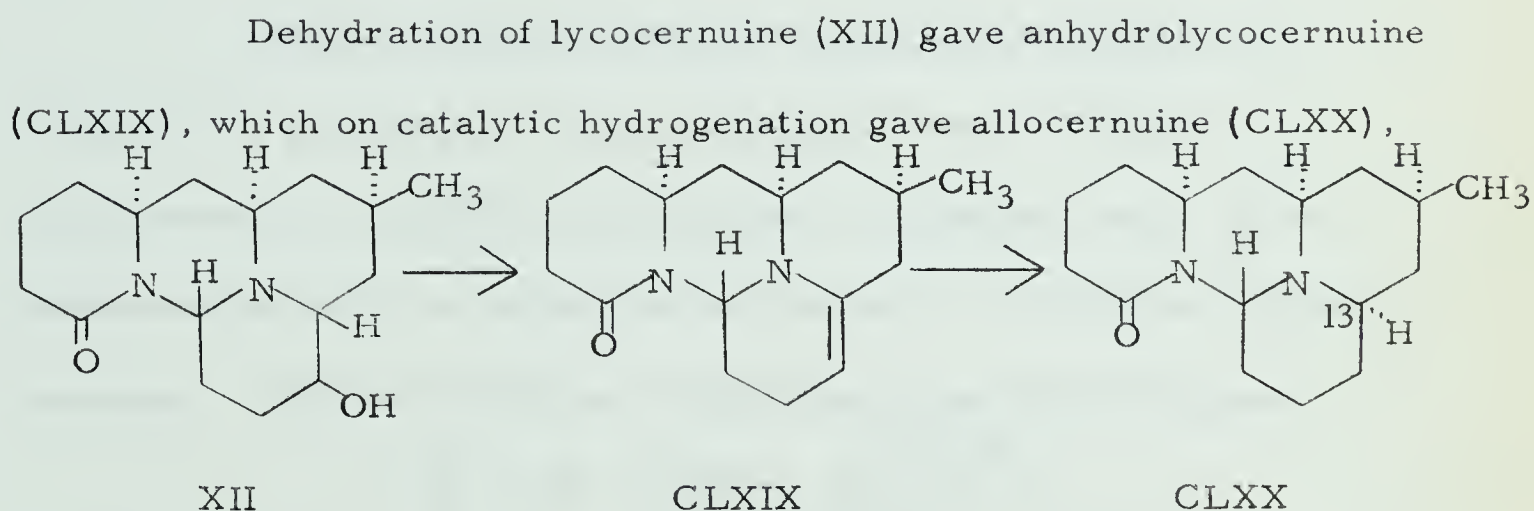
CLXVII



CLXVIII

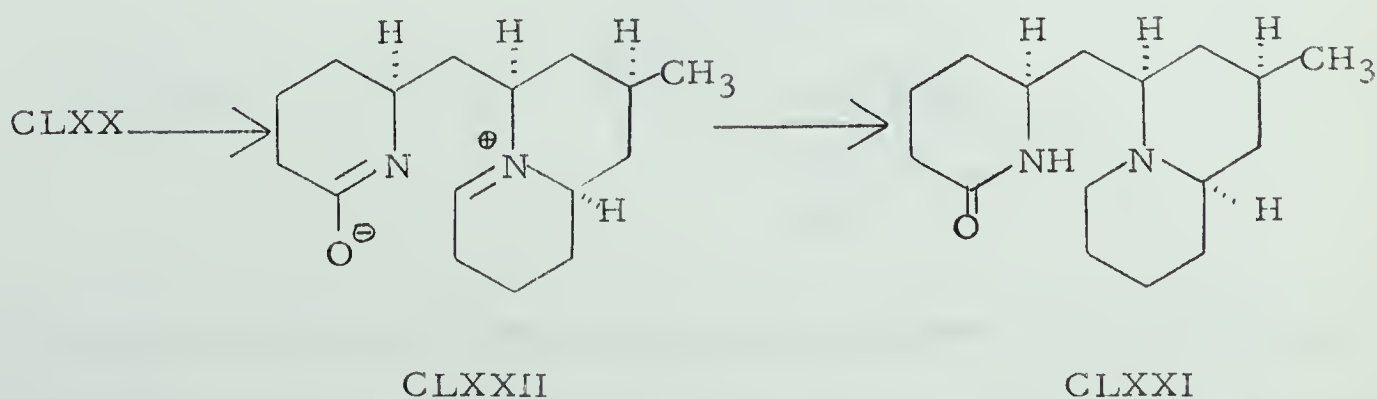
group is now confirmed by the total synthesis of dihydrodeoxyepiallocernuine (CL).

Since the transformation of lycocernuine (XII) into dihydrodeoxyepiallocernuine (CL) must involve isomerization at only two centers (see below), C-9 and C-13, the total synthesis of dihydrodeoxyepiallocernuine (CL) also confirms the stereochemical assignment made for cernuine (XI) and lycocernuine (XII) at the centers C-5 and C-7.

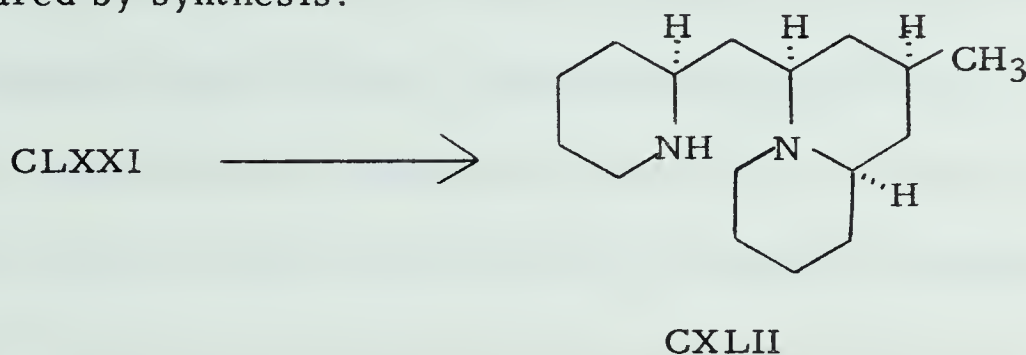


epimeric with cernuine at C-13. As expected allocernuine did not show "Bohlmann bands" in the infrared.

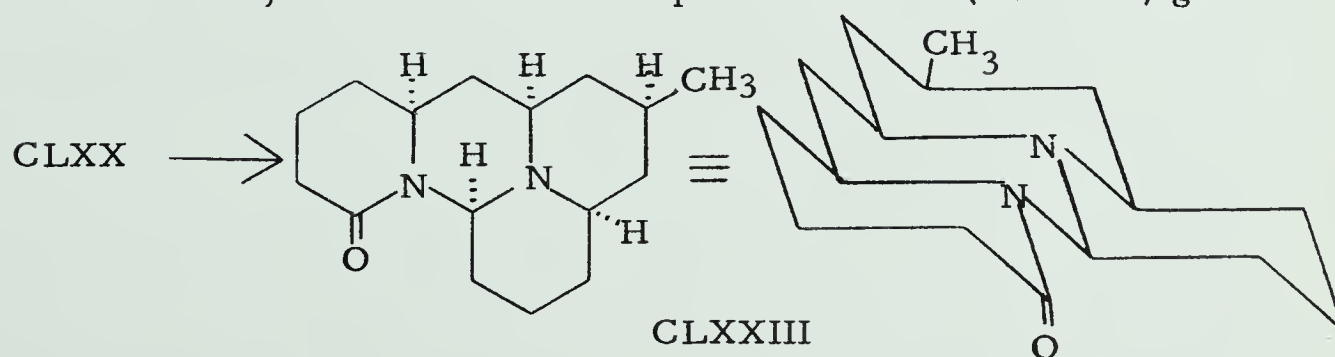
Sodium borohydride reduction of allocernuine (CLXX) gave the ring-opened compound CLXXI presumably formed via the intermediate



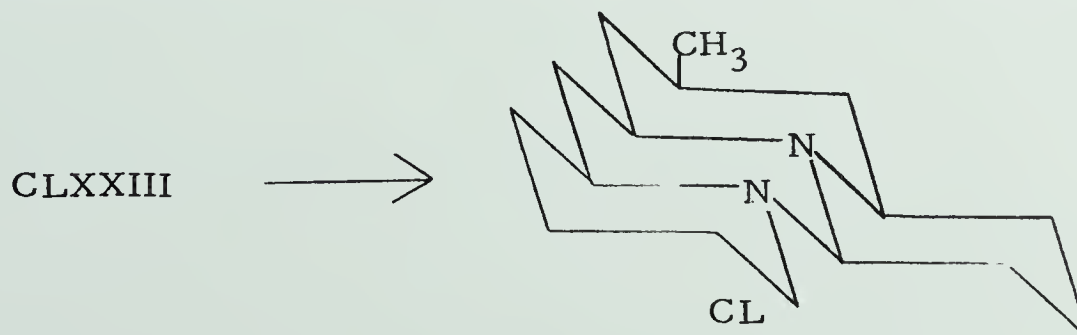
immonium salt CLXXII. Lithium aluminum hydride reduction of CLXXI gave the tricyclic N-H compound CXLII which has now been prepared by synthesis.



By refluxing in methanol, alloceruine (CLXX) was isomerized, presumably via the zwitterionic form CLXXII, to epialloceruine (CLXXIII), which showed "Bohlmann bands" in the infrared spectrum, in agreement with structure CLXXIII for epialloceruine. Hydride reduction of epialloceruine (CLXXIII) gave



dihydrodeoxyepialloceruine (CL) which has now also been obtained



in the total synthesis of the ceruine ring skeleton. Dihydrodeoxyepialloceruine (CL) was also obtained directly from alloceruine (CLXX)

by lithium aluminum hydride reduction.

The original objective of achieving a total synthesis of the cernuine ring skeleton has been achieved, proving that the structural assignment made (15) for cernuine and lycocernuine is correct. The fact, that dihydrodeoxyepiallocernuine (CL) has been obtained in the total synthesis also confirms the stereochemical assignment made for the alkaloids cernuine (XI) and lycocernuine (XII) at C-5, C-7 and C-15 and also proves the relative stereochemistry of dihydrodeoxyepiallocernuine (CL).

EXPERIMENTAL

Nuclear magnetic resonance spectra were measured in deuterio-chloroform solution unless otherwise specified, using a Varian Associates Model A-60 spectrometer or a Varian Associates Model HR-100 spectrometer with tetramethylsilane as an internal standard.

Infrared spectra were recorded on a Perkin-Elmer Model 421 dual grating infrared spectrophotometer or a Perkin-Elmer Model 337 grating infrared spectrophotometer.

Mass spectra were recorded on an A.E.I. Model MS-2H or an A.E.I. Model MS-9 mass spectrometer.

Melting points were determined on a hot-stage Fischer-Johns melting point apparatus and are uncorrected.

Alumina, unless otherwise specified, means basic alunina of activity III-IV (Brockman scale).

Research Specialty Company Aluminum Oxide G was used for thin layer chromatography.

Microanalyses are by C. Daessle, Montreal, Quebec.

THE ENOL ETHER OF 2,4-PENTANEDIONE

The enol ether of 2,4-pentanedione was prepared according to the procedure give by Claisen (63). A mixture of 2,4-pentanedione (75 g, 0.75 mole), ethyl orthoformate (71 g, 0.48 mole), 98% ethanol (69 cc) and ferric chloride (2.3 g, 0.014 mole) was heated at reflux

temperature for ten minutes. After cooling, the reaction mixture was poured into ice cold aqueous sodium hydroxide and the mixture was immediately shaken with ether. The ether solution was washed with aqueous sodium hydroxide until a neutralized portion of the basic extracts no longer showed a color with ferric chloride solution. The ether solution was then washed once with water and dried over anhydrous sodium sulfate. The ether was distilled off and the enol ether of 2,4-pentanedione was distilled at reduced pressure (33 g, b.p. 56°C/4mm).

REACTION OF PICOLYL LITHIUM WITH THE ENOL ETHER OF 2,4-PENTANEDIONE

A dry three-necked flask was equipped with a dropping funnel, a stirrer and a reflux condenser protected from atmospheric moisture and the system was swept with a slow stream of nitrogen. Anhydrous ether (400 ml) and small pieces of lithium metal (6.9 g, 1 g-atom) were placed in the flask and stirring was begun. About ten ml of a solution of bromobenzene (75 g, 0.5 mole) in ether (100 ml) was added all at once from the dropping funnel. After the reaction had begun the remainder of the bromobenzene solution was added at such a rate that the ether constantly boiled. After complete addition of the bromobenzene the reaction mixture was refluxed until all the lithium had reacted (about five hours).

To a stirred solution of phenyllithium, redistilled α -picoline

(46 g, 0.45 mole) was added dropwise and the stirring was continued at room temperature for five hours. The reaction mixture was now dark red-brown in color.

A solution of the enol ether of 2,4-pentanedione (32 g, 0.25 mole) in ether (70 ml) was added dropwise to the ethereal solution of picolyl lithium at 0°C. After complete addition the reaction mixture was stirred at room temperature for one hour and then ice and water were added. The product was extracted with ether and distillation gave the basic enol ether CIV, b.p. 112-114°C/0.7 mm. Lit. b.p. 108-116°C/0.5 mm (56).

The N.M.R. spectrum of the enol ether showed signals at τ 8.85 (3H, triplet, $J=7$ cps, $\text{CH}_3\text{-CH}_2\text{-O-}$), τ 6.47 (2H, quartet, $J=7$ cps, $\text{CH}_3\text{-CH}_2\text{-O-}$), τ 8.6 (3H, singlet, $\text{CH}_3\text{-COH}$), τ 7.9 (3H, singlet, $\text{CH}_3\text{-}\overset{\text{OEt}}{\text{C}}=\text{C-}$), τ 6.9 (2H, singlet $\text{Ar-CH}_2\text{-CO}$), τ 4.2 (1H, singlet, H-C=C-), τ 1.3-2.9 (4H, Ar-H).

2,4-DIMETHYLQUINOLIZINIUM PICRATE

The enol ether CIV (1 g) was dissolved in ethanol containing excess picric acid and the solution was boiled for ten minutes. The 2,4-dimethylquinolizinium picrate crystallized on cooling. Recrystallization from ethanol gave yellow crystals m.p. 154-155°C. Lit. m.p. 150-151°C (56).

THE 2,4-DIMETHYLQUINOLIZINIUM IODIDE XCV

A solution of the enol ether CIV (1 g) in 95% ethanol (10 ml)

containing freshly distilled hydriodic acid (2 g) was refluxed for 90 minutes. Upon cooling a crop of yellow crystals precipitated. Recrystallization from 95% ethanol gave the pure 2,4-dimethylquinolizinium iodide XCV as colorless crystals, m.p. 207-208°C.

The N.M.R. spectrum of the salt in ethylene carbonate solution showed signals at τ 7.3 (3H, singlet), τ 6.9 (3H, singlet) and τ 0.5 to 2.0 (6H, multiplet) and at τ 7.6 (3H, singlet), τ 7.3 (3H, singlet) and τ 1.5 to 2.6 (6H, multiplet) in trifluoroacetic acid solution.

α -PICOLINE METHIODIDE

The methiodide of α -picoline was prepared by refluxing a solution of α -picoline in methanol with excess methyl iodide for thirty minutes. The solid which formed on cooling was recrystallized from ethanol to give α -picoline methiodide as colorless needles, m.p. 229-230°C.

The N.M.R. spectrum of α -picoline methiodide in ethylene carbonate solution showed signals at τ 7.12 (3H, singlet) and τ 5.7 (3H, singlet) as well as signals for four aromatic protons between τ 0.9 and 2.2.

γ -PICOLINE METHIODIDE

The methiodide of γ -picoline was prepared by refluxing a solution of γ -picoline in methanol with excess methyl iodide for thirty minutes. Ether was then added to the cloud-point and the solid which formed on cooling was recrystallized from acetone to yield γ -picoline

methiodide as off-white crystals, m.p. 151-152°C.

The N.M.R. spectrum of γ -picoline methiodide in ethylene carbonate showed signals at τ 7.3 (3H, singlet) and τ 5.6 (3H, singlet) and τ 2.0 (2H, doublet, $J=12$ cps) and τ 1.0 (2H, doublet, $J=12$ cps).

CONDENSATION OF THE 2,4-DIMETHYLQUINOLIZINIUM IODIDE X CV WITH p-DIMETHYLAMINO BENZALDEHYDE

To a solution of the quinolizinium iodide XCV (0.3 g, 1.05 mmole) and p-dimethylaminobenzaldehyde (0.31 g, 2.1 mmole) in absolute ethanol (5 ml) was added three drops of piperidine and the reaction mixture was refluxed for five hours. The crystalline material which had separated was removed by filtration and dried.

The N.M.R. spectrum in trifluoroacetic acid solution showed signals at τ 7.26 (3H, singlet), τ 6.9 and τ 7.0 (6H, 2 singlets) and τ 1.5 to τ 2.9 (12H, multiplet).

GLUTARIMIDE

Glutarimide was prepared according to the procedure given in Organic Synthesis (62).

In a three-necked flask fitted with a mechanical stirrer and a reflux condenser (fume hood) were placed γ -butyrolactone (36 g, 1 mole) and potassium cyanide (72 g, 1.1 mole). The stirred reaction mixture was heated at 190-195°C for two hours using an oil bath and then was allowed to cool to 100°C. The potassium salt of the cyano acid thus formed was dissolved in water (200 ml) and the reaction

mixture was carefully acidified with concentrated hydrochloric acid (90 ml). The resulting solution was extracted with ether (six times 50 ml) and the combined ether extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the oily residue of glutaric acid monoamide was heated on the oil bath at 220-225°C until no more water distilled from the reaction mixture (approx. four hours). The cooled reaction mixture was taken up in water (200 ml) and boiled with activated charcoal (2 g) for thirty minutes. The charcoal was removed by filtration and the water was removed under reduced pressure. The dry residues were recrystallized from 95% ethanol yielding glutarimide as glittering white crystals, m.p. 153-154°C.

TRIETHYLOXONIUM FLUOBORATE

Triethyloxonium fluoborate was prepared according to the procedure described by Meerwein (61).

In a three-necked flask fitted with a mechanical stirrer, dropping funnel and a reflux condenser was placed freshly distilled boron trifluoride-etherate (152 g, 1.07 mole) in anhydrous ether (400 ml). Epichlorohydrin (81.6 g, 0.88 mole) was then added with vigorous stirring at such a rate that the ether constantly boiled. After complete addition of the epichlorohydrin the reaction mixture was stirred for an additional two hours and then was allowed to stand at room temperature for fourteen hours. The fluoborate salt which separated

as a colorless solid was removed by filtration through a sintered glass funnel under a stream of nitrogen. The salt was then washed with four portions of ether (50 ml each) and then stored in the cold under dry ether.

ATTEMPTED PREPARATION OF GLUTARIMIDE MONO-IMINOESTER C

A. Reaction of Glutarimide with triethyloxonium fluoborate.

Glutarimide was recovered unchanged after treatment under the following conditions:

i) reaction of glutarimide with triethyloxonium fluoborate in methylene chloride at 0°C for three hours.

ii) reaction of glutarimide with triethyloxonium fluoborate in methylene chloride at room temperature for forty-eight hours.

iii) reaction of glutarimide with triethyloxonium fluoborate in methylene chloride at reflux temperature for eighteen hours.

iv) reaction of glutarimide with a large excess of triethyloxonium fluoborate in methylene chloride at reflux temperature for twenty hours.

B. Reaction of Glutarimide with sodium hydroxide, silver nitrate and ethyl iodide.

i) In diethyl ether

To a solution of glutarimide (5 g, 44 mmole) and sodium hydroxide (1.76 g, 44 mmole) in water (80 ml) was added silver nitrate (7.48 g, 44 mmole). The colorless solid which precipitated immediately

was filtered off and washed with water and alcohol. The solid was dissolved in ether and shaken in the dark with ethyl iodide (6.80 g, 44 mmole) for twenty hours. The precipitate in the reaction flask was then filtered off and washed with ethanol containing a few ml. of hydrochloric acid. The combined filtrates were evaporated to dryness and the residues were taken up in 5% aqueous potassium carbonate solution. Chloroform extraction gave colorless crystalline material (0.5 g) which proved to be the monoethyl ester monoamide of glutaric acid.

The infrared spectrum showed absorption at 3520 and 3410 cm^{-1} (strong, sharp, N-H), 1725 cm^{-1} (ester) and 1680 and 1590 cm^{-1} (amide I and amide II absorption) in chloroform.

The N.M.R. spectrum showed signals at τ 8.8 (3H, triplet $J=7$ cps) ($\text{CH}_3\text{-CH}_2\text{-O-}$), τ 5.85 (2H, quartet, $J=7$ cps, $\text{CH}_3\text{-CH}_2\text{-O-}$), τ 3.6 (2H br. singlet, -NH_2) and an eight proton multiplet between τ 7.4 and τ 8.2.

ii) In glyme

Glutarimide (5 g, 44 mmole) was dissolved in cold water (50 ml) containing sodium hydroxide (1.76 g, 44 mmole) and silver nitrate (7.48 g, 44 mmole) was added. The silver salt which precipitated was filtered off, washed with water and alcohol and then was dissolved in glyme (125 ml). Ethyl iodide (10 g, 64 mmole) was added and the solution was shaken in the dark for twenty-one hours. The precipitate

which formed was removed by filtration and washed with chloroform. The combined filtrates were dried over anhydrous magnesium sulfate and evaporated giving colorless crystalline material (5 g) which was identical with the monoester monoamide of glutaric acid obtained above.

VALEROLACTAM IMINOESTER CVI

To a solution of freshly distilled δ -valerolactam (b.p. $84^{\circ}\text{C}/0.5\text{ mm}$) (31 g, 0.31 mole) in methylene chloride (150 ml) was added all at once a solution of triethyloxonium fluoborate (89 g, 0.47 mole) in methylene chloride (100 ml) and the resulting solution was stirred at room temperature for fifteen hours. The reaction mixture was poured into 5N aqueous potassium carbonate and extracted thoroughly with methylene chloride. The solvent was evaporated. Distillation of the residue furnished the pure iminoester CVI of valerolactam (b.p. $45^{\circ}\text{C}/7\text{ mm}$).

The infrared spectrum in chloroform showed a strong absorption band at 1670 cm^{-1} .

The N.M.R. spectrum displayed signals at τ 7.75 (3H, triplet, $J=7\text{ cps}$, $\text{CH}_3\text{-CH}_2\text{-O-}$), τ 5.95 (2H, quartet, $J=7\text{ cps}$, $\text{CH}_3\text{-CH}_2\text{-O-}$), τ 6.5 (2H, triplet, $\text{CH}_2\text{-CH}_2\text{-N}$) and τ 7.7 to τ 8.5 (6H, multiplet).

CONDENSATION OF THE MONO-LITHIUM SALT OF 2,4-LUTIDINE WITH THE IMINOESTER CVI OF VALEROLACTAM

The mono lithium salt of 2,4-lutidine was prepared

according to the procedure given in the literature (64).

To a solution of phenyllithium (from bromobenzene (52 g, 0.33 mole) and lithium metal (4.6 g, 0.66 g-atom) in anhydrous ether (300 ml) was added freshly distilled 2,4-lutidine (42.6 g 0.34 mole) and the resulting solution was stirred at room temperature for two hours. To the resulting dark red-brown reaction mixture was added dropwise a solution of the iminoester CVI of valerolactam (35.7 g, 0.28 mole) in dry benzene (80 ml) and the reaction mixture was then refluxed for eighteen hours. The cooled solution was then poured into aqueous (10%) potassium carbonate solution and the product was extracted thoroughly with chloroform.

The crude product was distilled under reduced pressure and the fraction boiling between 123-132°C/0.4 mm was collected. The material so obtained was normally subjected to the next reaction without further purification.

A portion of the crude distillation product was subjected to column chromatography on florisil. Elution with benzene-ether (3:2) gave a two component mixture which appeared to consist of double bond isomers of the desired olefinic piperidylpyridine CVII compound.

The infrared spectrum in chloroform contained absorption bands at 3200 cm^{-1} (N-H) and 1650 cm^{-1} (medium, sharp), 1610 , 1600 , 1590 cm^{-1} (strong, sharp).

2-(2-PIPERIDYLMETHYL)-4-METHYLPYRIDINE (CVIII)

The crude distilled product (5 g) obtained from condensation of lutidyllithium with the iminoester of valerolactam was dissolved in methanol (20 ml). Palladium-charcoal (300 mg) was added and the contents of the flask were subjected to hydrogenation at atmospheric pressure until uptake of hydrogen was complete. The catalyst was removed by filtration and the solvent was evaporated at the pump. The residues were chromatographed on alumina (100 g). Elution with chloroform-ether (2:1) furnished 2-(2-piperidylmethyl)-4-methylpyridine (CVIII) as a pale yellow oil.

The infrared spectrum in carbon tetrachloride showed a concentration independent band at 3320 cm^{-1} , and aromatic absorption at 3060, 3020 and 1600 cm^{-1} .

The N.M.R. spectrum revealed significant signals at τ 7.7 (3H, singlet), τ 2.5-3.1 (2H) and τ 1.5 (1H, doublet).

The mass spectrum had a parent peak at m/e 190 with the major peaks appearing at m/e 107 (70%) and m/e 84 (100%).

THE N-FORMYL COMPOUND CXI

Mixed acetic-formic anhydride was prepared by warming a mixture of acetic anhydride (20.4 ml) and 98% formic acid (8.6 ml) at $50-60^{\circ}\text{C}$ for two hours.

To a portion of the mixed anhydride (19.0 ml) in a dry reaction flask was added a solution of 2-(2-piperidylmethyl)-4-methyl-

pyridine (3.8 g) in anhydrous ether (150 ml). The reaction mixture was stirred at room temperature for three hours and was then poured into aqueous (10%) potassium carbonate solution and shaken for ten minutes. Chloroform extraction furnished a pale yellow oil which showed a single spot on thin layer chromatography.

Distillation furnished the pure N-formyl compound CXI
b.p. $156-158^{\circ}\text{C}/0.3\text{ mm}$.

The infrared spectrum in carbon tetrachloride showed aromatic absorption at 3050 cm^{-1} (weak) and 1600 cm^{-1} (strong) and a strong band at 1665 cm^{-1} (N-formyl).

The N.M.R. spectrum revealed the expected signals at τ 7.7 (3H, singlet), τ 2.0 and τ 2.2 (1H, two singlets, $-\text{CHO}$, rotameric forms) as well as three aromatic protons between τ 1.6 and τ 3.15.

The mass spectrum revealed a parent peak at m/e 218 with other significant peaks at m/e 189 (44%), m/e 112 (96%), m/e 107 (100%) and m/e 84 (76%).

HYDROLYSIS OF THE N-FORMYL COMPOUND CXI

A. In 5% sulfuric acid

A solution of the N-formyl compound CXI (130 mg) in 5% sulfuric acid (10 ml) was refluxed for two hours and then cooled and poured into cold aqueous ammonium hydroxide. Chloroform extraction gave a pale yellow oil (108 mg) which was identical with the 2-(2-piperidyl-methyl)-4-methylpyridine (CVIII).

B. In 10% potassium hydroxide

A solution of the N-formyl compound CXI (125 mg) in 10% potassium hydroxide was refluxed for three hours. The cooled reaction mixture was extracted thoroughly with chloroform yielding a pale yellow oil (100 mg) which was identical with the 2-(2-piperidylmethyl)-4-methylpyridine (CVIII).

ATTEMPTED PREPARATION OF δ -BROMOBUTYRALDEHYDE

A. Reaction of δ -bromobutyronitrile with lithium triethoxyaluminum hydride

δ -Bromobutyronitrile was reacted under the conditions described by Brown (69).

To a solution of lithium aluminum hydride (1 g, 26 mmole) in anhydrous ether (60 ml) under dry nitrogen at -7°C was added ethyl acetate (3.5 g, 29 mmole) over a period of twenty minutes and stirring was continued for an additional fifteen minutes. Then δ -bromobutyronitrile (3.9 g, 26 mmole) was added to the reaction mixture and stirring was continued at 0°C for one hour. Sulfuric acid (5N, 50 ml) was added and the aqueous phase was thoroughly extracted with ether. Evaporation of the ether led to recovery of starting material (3 g).

The above procedure was repeated except that the reaction mixture was refluxed for twenty hours. Workup as before led to a liquid which showed only weak carbonyl absorption in the infrared spectrum and appeared to be mainly starting material.

B. Reaction of γ -bromobutyronitrile with lithium aluminum hydride

To a solution of lithium aluminum hydride (100 mg, 2.6 mmole) in anhydrous ether (10 ml) at 0°C was added γ -bromobutyronitrile (1.24 g, 10.5 mmole) in dry ether (10 ml). Stirring was continued at 0°C for two hours and then sulfuric acid (5N, 30 ml) was added. Ether extraction of the aqueous phase led to the recovery of starting material.

C. Reduction of γ -bromobutyronitrile with stannous chloride

γ -Bromobutyronitrile was subjected to the conditions of the Stephens reduction (70).

Dry hydrogen chloride gas was bubbled through a solution of anhydrous stannous chloride (7.8 g, 41 mmole) in dry ether (30 ml) until two clear liquid layers had separated.

γ -Bromobutyronitrile (4 g, 27 mmole) was added rapidly and the reaction mixture was stirred vigorously for one hour and thirty minutes. When no precipitate had formed after this time the reaction mixture was heated on the steam bath for eight hours. The reaction mixture was then hydrolyzed with boiling water for two hours. Ether extraction of the aqueous phase failed to give the desired product.

REACTION OF γ -BROMOBUTYRONITRILE WITH HYDROGEN CHLORIDE AND ETHANOL

γ -Bromobutyronitrile (7.64 g, 0.052 mole) was dissolved in absolute ethanol (3.3 ml, 0.057 mole) and dry hydrogen chloride gas was bubbled through the cooled solution until 2.07 g (0.057 mole) had

been absorbed. The reaction mixture was allowed to stand in the refrigerator for twenty hours after which time it had solidified into a colorless cake. Ether was added and the solid was ground into a fine powder and filtered. The solid was twice triturated under cold ether and then it was dried in a vacuum dessicator. The iminoester hydrochloride of γ -bromobutyronitrile (CXII) was formed in almost quantitative yield.

The infrared spectrum of the salt in Nujol revealed intense broad absorption between 3200 and 2600 cm^{-1} as well as a strong band at 1645 cm^{-1} .

ALCOHOLYSIS OF THE IMINOESTER HYDROCHLORIDE OF γ -BROMO-BUTRALDEHYDE CXII

The iminoester hydrochloride (5 g, 0.022 mole) was suspended in a mixture of absolute ethanol (18.5 ml, 0.314 mole) and anhydrous ether (55 ml) and the mixture was refluxed for fifteen hours (b.p. 39°C) and then cooled to 0°C. The ammonium chloride which had precipitated during the reaction was removed by filtration and washed with ether. The combined filtrates were washed first with 10% sodium carbonate solution and then with a saturated sodium carbonate solution. The organic phase was dried over anhydrous potassium carbonate and the solvent was removed at the pump.

The crude product so isolated appeared to be a mixture of the expected orthoester of γ -bromobutyric acid and the normal carboxylic

ester, ethyl- γ -bromobutyrate.

Attempted purification of the triethylorthoester by distillation led to decomposition to the carboxylic ester as indicated by the infrared spectrum.

Attempted removal of the carboxylic ester by hydrolysis in aqueous 10% potassium hydroxide was unsuccessful as the product isolated from the hydrolysis always contained carbonyl impurities.

THE IMINOESTER HYDROCHLORIDE CXIII OF γ -CHLOROBUTYRO - NITRILE

Dry hydrogen chloride gas was bubbled through a cooled solution of γ -chlorobutyronitrile (20 g, 0.193 mole) in absolute ethanol (9.8 g, 0.21 mole) until 7.78 g (0.21 mole) had been absorbed and the resulting solution was allowed to stand in the cold for four hours after which time it had solidified. Ether was added and the solid cake was ground up into a fine powder, and the ether was removed by filtration. The salt was triturated twice with cold (-30°C) ether and then dried in a vacuum dessicator, yield 35 g.

The iminoester hydrochloride CXIII showed strong infrared absorption between 3200 and 2800 cm^{-1} as well as a strong band at 1645 cm^{-1} .

TRIETHYLORTHOESTER CXIV OF γ -CHLOROBUTYRIC ACID

The iminoester hydrochloride CXIII of γ -chlorobutyronitrile (5 g, 0.027 mole) was dissolved in absolute ethanol (22.8 ml, 0.39 mole)

and anhydrous ether (45 ml) was added. The reaction mixture was refluxed for sixteen hours and then was cooled to 0°C. The ammonium chloride which had formed during the reaction was removed by filtration and washed with a small portion of ether. The combined filtrates were washed with two portions (50 ml) of saturated sodium carbonate solution and the ether layer was dried over anhydrous potassium carbonate. Removal of solvents gave a colorless liquid which showed only minor traces of carbonyl containing material in the infrared spectrum.

Saponification of this liquid with 10% aqueous alcoholic potassium hydroxide (30 ml water, 20 ml ethanol) at 55°C for eighteen hours gave the triethylorthoester CXIV of γ -chlorobutyric acid (4.5 g) which was now free of carbonyl containing impurities.

The orthoester showed intense infrared absorption between 1050 and 1100 cm^{-1} in carbon tetrachloride.

The N.M.R. spectrum contained the expected signals at τ 8.8 (9H, triplet, $J = 9$ cps), τ 8.0-8.4 (4H, multiplet) and τ 6.5 (8H, quartet, $J = 9$ cps).

THE DIETHYLACETAL CXV OF γ -CHLOROBUTYRALDEHYDE

To a solution of the triethylorthoester CXIV of γ -chlorobutyric acid (44 g, 0.195 mole) in dry benzene (500 cc) was added a solution of lithium aluminum hydride (2.47 g, 0.065 mole) in diethyl ether (65 ml). The reaction mixture was refluxed for seven hours and was then cooled to 0°C. A 30% aqueous solution of sodium potassium

tartrate (200 ml) was added and the mixture was shaken thoroughly. The benzene layer was separated and the aqueous phase was washed once with ether. The combined organic extracts were dried over anhydrous potassium carbonate and the solvents were removed at the pump. Distillation of the residues gave the diethylacetal CXV of γ -chlorobutyraldehyde (31 g) b.p. $59-60^{\circ}\text{C}/2\text{ mm}$.

A portion of the acetal was treated with 2,4-dinitrophenylhydrazine reagent to give the corresponding 2,4-dinitrophenylhydrazone of γ -chlorobutyraldehyde. m.p. $130-131^{\circ}\text{C}$, Lit. m.p. $130^{\circ}-131^{\circ}\text{C}$ (75).

The infrared spectrum of the acetal in carbon tetrachloride displayed strong bands at 1130 cm^{-1} and 1070 cm^{-1} .

The N.M.R. spectrum revealed signals at τ 8.8 (6H, triplet, $J=10\text{ cps}$), τ 8.1-8.4 (4H, multiplet), τ 6.2-6.6 (6H, multiplet) and τ 5.5 (1H, triplet).

ATTEMPTED REACTION OF THE γ -CHLOROBUTYRALDEHYDE DIETHYLACETAL CXV WITH LITHIUM METAL

The chloroacetal CXV failed to react detectably with lithium metal under the following conditions.

- i). in anhydrous ether at room temperature for sixteen hours
- ii) in anhydrous ether at the reflux temperature for forty hours
- iii) in dry isopentane (b.p. 28°C) at the reflux temperature for eighteen hours

iv) in dry petroleum ether (b.p. 66°C) at the reflux temperature for twenty-two hours.

REACTION OF THE GRIGNARD REAGENT CXVI OF γ -CHLORO-
BUTYRALDEHYDE DIETHYLACETAL WITH THE N-FORMYL
COMPOUND CXI

A. Reaction of γ -chlorobutyraldehyde diethylacetal CXV with magnesium metal in tetrahydrofuran.

The chloroacetal (20.0 g, 0.111 mole) was added dropwise to vigorously stirred tetrahydrofuran (50 ml) (dried over lithium aluminum hydride) containing magnesium metal (2.43 g, 0.1 mole) while heating at reflux temperature. Methyl iodide (3 drops) was added to initiate the reaction and after complete addition of the chloroacetal the reaction mixture was refluxed for eight hours after which time no magnesium metal remained and the solution was dark in color.

B. Reaction of the Grignard CXVI with the N-formyl compound CXI

To a solution of the Grignard reagent prepared as above was added a solution of the N-formyl compound CXI (6 g, 0.028 mole) in dry tetrahydrofuran (10 ml) and resulting solution was refluxed for four hours. Water (200 ml) was added to the reaction mixture and the crude product was extracted with chloroform which was removed at the pump. After bubbling air through the crude reaction product the low boiling materials were removed by distillation. The residue of the distillation was a viscous black tarry material, thin layer chromato-

graphic analysis of which revealed at least five basic components. No characterizable material could be isolated from this tar.

THE PYRIDINE N-OXIDE CXX

To a solution of the N-formyl compound CXI (1.3 g, 6.4 mmole) in chloroform (15 ml) was added m-chloroperbenzoic acid (1.55 g, 9.0 mmole) and the reaction mixture was stirred at room temperature for twenty-four hours. The reaction mixture was shaken with 5% sodium bisulfite solution and was then washed with two portions of saturated sodium bicarbonate solution. The chloroform layer was dried over anhydrous magnesium sulfate and evaporated. The pyridine N-oxide CXX so obtained was homogenous on thin layer chromatography and appeared as a colorless viscous oil.

The N-oxide CXX had infrared bands at 3650 cm^{-1} (weak), 1610 cm^{-1} (pyridine) and 1240 cm^{-1} (strong, N-oxide) in carbon tetrachloride.

REACTION OF THE PYRIDINE N-OXIDE CXX WITH THE GRIGNARD REAGENT CXVI OF γ -CHLOROBUTYRALDEHYDE DIETHYLACETAL

A. With one equivalent of the Grignard reagent CXVI

The Grignard reagent from γ -chlorobutyraldehyde diethylacetal CXV (2.07 g, 11.5 mmole) and magnesium metal (0.27 g, 11.0 mmole) in tetrahydrofuran was prepared as above. A solution of the pyridine N-oxide CXX (2.35 g, 10 mmole) in dry tetrahydrofuran (10 ml) was added rapidly to the Grignard reagent at 0°C . Immediately upon

addition of the N-oxide CXX a thick cream colored precipitate formed. The reaction mixture was stirred at room temperature for sixteen hours then water (50 ml) was added. Chloroform extraction yielded a dark brown oil which proved to be the starting pyridine N-oxide CXX.

The above reaction was repeated using pyridine N-oxide CXX which had been refluxed in dry benzene using a water separator in an effort to dry the N-oxide prior to addition to the Grignard reagent. When pyridine N-oxide so treated was used in the reaction with the Grignard reagent, starting material was again obtained.

B. With excess Grignard reagent

To a solution of the Grignard reagent CXVI prepared from γ -chlorobutyraldehyde diethylacetal CXV (14.4 g, 80 mmole) and magnesium metal (1.89 g, 77 mmole) in dry tetrahydrofuran (100 ml), was added a solution of the pyridine N-oxide CXX (3 g, 13 mmole) in tetrahydrofuran and the reaction mixture was refluxed for eighteen hours. Water (200 ml) was added to the cooled reaction mixture. Chloroform extraction of the aqueous phase gave a brown colored liquid. The low boiling components were removed by distillation.

The residue, now a viscous brown oil, did not show any distinct spots on thin layer chromatography. No characterizable product could be obtained either from column chromatography or from acid-base extraction to separate basic, neutral and acidic components.

ATTEMPTED PREPARATION OF THE 2-(2-PIPERIDYLMETHYL)-
4-METHYL-6-CYANOPYRIDINE CXXIV

Dimethyl sulfate (0.57 g, 4.5 mmole) was added to the pyridine N-oxide CXX (1.01 g, 4.5 mmole) and the mixture was stirred until solution was complete. The reaction mixture was then heated on the steam bath for two hours. On cooling, the viscous oil solidified into a gummy material. The solid so obtained was dissolved in water (5 ml) and to this solution was added slowly a solution of potassium cyanide (0.78 g, 12 mmole) in water (5 ml) at 0°C with stirring under nitrogen. The reaction mixture was stirred at 0°C for one hour, then was allowed to warm to room temperature where stirring was continued for six hours. The product was extracted with chloroform.

The product so obtained showed five spots on thin layer chromatography but did not show any traces of nitrile absorption in the infrared spectrum and was not further characterized.

REACTION OF THE MONOLITHIUM SALT OF 2,4,6-COLLIDINE WITH
ACROLEIN

To a solution of phenyllithium prepared as before from lithium metal (2.78 g, 0.4 g-atom) and bromobenzene (31.4 g, 0.2 mmole) in anhydrous ether was added freshly distilled 2,4,6-collidine (26.6 g, 0.22 mmole) and the resulting solution was stirred at room temperature for four hours. The reaction mixture was transferred to an addition

funnel and added dropwise to a cold stirred solution of acrolein (19.5 ml, 16.8 g, 0.3 mole) in dry ether (100 ml) in an atmosphere of nitrogen. An instantaneous reaction appeared to take place as indicated by the loss of color of the collidyllithium solution and the formation of a colorless precipitate. Addition was complete in two and one half hours and the reaction mixture was stirred at 0°C for an additional five hours. Water (200 ml) was carefully added and, after shaking, the ether layer was separated. The aqueous phase was washed with two small portions of chloroform and the combined organic extracts were extracted six times with dilute hydrochloric acid. The combined acidic aqueous extracts were basified with cold aqueous ammonium hydroxide and extraction with chloroform yielded the basic components of the reaction mixture.

The crude product so obtained had infrared absorption in carbon tetrachloride at 3600 and 3400 cm^{-1} (broad) (hydroxyl) and 1600 and 1550 cm^{-1} (pyridine) with no absorption in the carbonyl region.

The N.M.R. spectrum contained aromatic proton signals (τ 3.2), olefinic proton signals (τ 4.0-5.2) and no aldehydic proton.

The product of the reaction was not further purified or characterized.

REACTION OF THE MONOLITHIUM SALT OF 2,4,6-COLLIDINE WITH ALLYL BROMIDE

The monolithium salt of 2,4,6-collidine (from 105 g,

0.87 mole of freshly distilled collidine) was prepared by reaction with one equivalent of phenyllithium in ether as before (see above). To the ethereal solution of collidyllithium at 0°C with stirring under nitrogen was added a solution of allyl bromide (107 g, 0.88 mole) in dry ether (150 ml). The rate of addition of allyl bromide was controlled so that the temperature did not rise above 10°C. After addition was complete (approximately two hours) the reaction mixture was stirred at 0-10°C for an additional two hours and then water (300 ml) was carefully added. The aqueous phase was extracted three times with ether and the combined organic extracts were washed thoroughly with dilute hydrochloric acid. Basification of the combined aqueous extracts with cold aqueous ammonium hydroxide followed by chloroform extraction gave the crude basic products of the reaction mixture.

The crude product was distilled under vacuum and the fraction with b.p. 54-56°C/0.5 mm was collected. This material proved to be pure 4,6-dimethyl-2-(3-butenyl)-pyridine CXXXVII.

The olefinic pyridine compound revealed infrared absorption in carbon tetrachloride at 3020, 1610, 1550 cm^{-1} (pyridine) and 3080, 1645, 990 and 910 cm^{-1} (vinyl).

The N.M.R. spectrum contained signals at τ 7.75 (3H, singlet), τ 7.5 (3H, singlet), τ 7.0-7.5 (4H), τ 3.8 to τ 5.2 (3H), and τ 3.2 (2H, singlet).

The mass spectrum had a parent peak at m/e 161 and the

base peak occurred at m/e 159.

The chloroplatinate of the product CXXVII was prepared in 10% hydrochloric acid and recrystallized from ethanol containing one drop of hydrochloric acid to give yellow needles m.p. 156-157.5°C.

The methiodide of the olefinic pyridine CXXVII was prepared in methanol and recrystallized from acetone-ether giving the methiodide as a colorless solid m.p. 111-113°C.

THE PYRIDINE ALCOHOL CXXVIII

The olefinic pyridine CXXVII (4.1 g, 0.025 mole) was dissolved in dry tetrahydrofuran (50 ml). Diborane, generated in a separate flask by the addition of a solution of sodium borohydride (2.0 g, 0.054 mole) in dry diglyme (20 ml) to a solution of freshly distilled boron trifluoride-etherate (14.5 g, 12.9 ml, 0.1 mole) in dry diglyme (80 ml), was passed into the reaction flask with a slow stream of nitrogen. After all the diborane had been generated (one hour) the reaction mixture was stirred for an additional two hours at room temperature. A few small pieces of ice were then added carefully to the cooled reaction mixture to decompose excess diborane.

A 3N solution of sodium hydroxide (15 ml) was added all at once to the reaction flask and then 30% hydrogen peroxide (15 ml) was added dropwise with cooling. After complete addition of the hydrogen peroxide the reaction mixture was stirred at room temperature for one hour and then was poured into water. The aqueous phase was

washed with ether (four times) and the combined ether extracts were thoroughly extracted with dilute hydrochloric acid. Basification of the acidic extracts with cold aqueous ammonium hydroxide followed by chloroform extraction gave a colorless liquid (4 g) which was homogenous on thin layer chromatography.

Distillation under reduced pressure furnished the pure pyridine alcohol CXXVIII, b.p. $110-112^{\circ}\text{C}/0.2\text{ mm}$, which solidified on cooling.

The alcohol displayed infrared bands at 3610 and 3400 cm^{-1} (broad) (hydroxyl) and at 1600 and 1560 cm^{-1} (aromatic) in carbon tetrachloride.

The N.M.R. spectrum revealed signals at the following positions: τ 8.1-8.5 (4H, multiplet), τ 7.75 (3H, singlet), τ 7.52 (3H, singlet), τ 7.25 (2H, triplet), τ 6.32 (2H, triplet), τ 5.9 (1H, broad) and τ 3.22 (2H, singlet).

The mass spectrum contained a parent peak at m/e 179 with other principle peaks at m/e 148 (92%), m/e 146 (73%), m/e 134 (100%) and m/e 121 (26%).

The p-nitrobenzoate of the alcohol was prepared in pyridine and was recrystallized from ethanol-water, m.p. $73-74^{\circ}\text{C}$.

ATTEMPTED OXIDATION OF THE PYRIDINE ALCOHOL CXXVIII TO THE ALDEHYDE CXX

A. With dimethyl sulfoxide and dicyclohexylcarbodiimide

The pyridine alcohol (0.5 g, 2.8 mmole) and dry dicyclo-

hexylcarbodiimide (1.73 g, 8.4 mmole) were dissolved in dimethylsulfoxide (dried over molecular sieves and distilled from calcium hydride under reduced pressure) and anhydrous phosphoric acid (0.41 g, 4.2 mmole) was added. After stirring at room temperature for eighteen hours the precipitate which had formed during the reaction was filtered off and washed well with ether. The combined filtrates were extracted thoroughly with dilute hydrochloric acid. Basification of the acidic extracts with ammonium hydroxide followed by chloroform extraction gave a brownish colored liquid (220 mg) which had an unpleasant odor.

The infrared spectrum in carbon tetrachloride was virtually devoid of absorption in the carbonyl region and revealed pyridine bands at 1600 and 1560 cm^{-1} as well as strong bands at 1100 and 1070 cm^{-1} .

The N.M.R. spectrum contained sharp singlets at τ 7.87 (3H), τ 7.75 (3H), τ 7.50 (3H), τ 5.4 (2H) and τ 3.2 (2H) in addition to triplets at τ 6.45 (2H) and τ 7.28 (2H) and a multiplet at τ 8.35 (4H).

On the basis of the above evidence it appeared that the thio-methyl ether CXXXI had formed.

B. With chromium trioxide in acetic acid

The pyridine alcohol (150 mg, 0.84 mmole) was dissolved in 95% acetic acid (40 ml) and the solution was cooled to 10°C. A solution of chromium trioxide (56 mg, 0.56 mmole) in 95% acetic acid (10 ml) was added dropwise to the cooled reaction mixture. After

addition was complete stirring was continued at 10°C for one hour and then at room temperature for fourteen hours. After this time the reaction mixture was poured into cold aqueous ammonium hydroxide. Chloroform extraction gave an oil which was composed of at least four components as shown by thin layer chromatography.

Bisulfite extraction of an ether solution of the oil failed to furnish any of the desired aldehyde CXXX.

THE PYRIDINE ACETAL CXXIV

To a solution of the pyridine alcohol CXXVII (56 g, 0.31 mole) in dry dimethoxyethane (100 ml) was added 3,4-dihydropyran (29.4 g, 0.35 mole) and dry hydrogen chloride was bubbled through the cooled solution until 12.8 g (0.35 mole) had been absorbed. The reaction mixture was stirred at room temperature for six hours and was then poured into cold aqueous ammonium hydroxide. Chloroform extraction gave a dark brown liquid. Distillation under reduced pressure furnished the pyridine acetal as a colorless liquid b.p. 130-132°C/0.5 mm. Calc. for $C_{16}H_{25}NO_2$: molecular wt., 263.1885. Found; 263.1880.

The pyridine acetal CXXXIV had infrared absorption bands in carbon tetrachloride at 1650 and 1560 cm^{-1} (pyridine) and several strong bands between 1020 and 1140 cm^{-1} (acetal).

The acetal CXXXIV displayed signals in the N.M.R. spectrum at τ 7.75 (3H, singlet), τ 7.52 (3H, singlet), τ 7.25 (2H, triplet),

τ 6.0-6.7 (4H, multiplet), τ 5.4 (1H, broad singlet) and τ 3.2 (2H, singlet).

THE PIPERIDYLPYRIDINE ACETAL CXXXVIII

To a solution of phenyllithium (from bromobenzene (12.6 g, 80 mmole) and lithium metal (1.11 g-atom) in ether (300 ml)) was added a solution of the pyridine acetal CXXXIV (20 g, 76 mmole) in ether (50 ml) and the reaction mixture was stirred at room temperature for four hours.

After four hours a small aliquot was extracted and plunged in deuterium oxide. The N.M.R. spectrum of the product so obtained was identical with that of the pyridine acetal except that the lower field methyl group at τ 7.52 now integrated for two protons instead of three.

A solution of the iminoester of valerolactam CVI (11.6 g, 100 mmole) in ether (30 ml) was added to the reaction mixture and stirring was continued at room temperature for forty hours. A few pieces of ice were then added to the reaction mixture followed by water (100 ml). The contents of the flask were then poured into aqueous potassium carbonate solution and extracted thoroughly with chloroform. Evaporation of the solvent gave a brown oil.

The low boiling components were removed by distillation under reduced pressure leading to a recovery of the excess iminoester CVI of valerolactam (approximately 6 g).

The residue, which had infrared absorption at 3200 cm^{-1}

(broad), 1620, 1600 and 1560 cm^{-1} and strong bands between 1020 and 1140 cm^{-1} , was dissolved in methanol and hydrogenated over palladium-charcoal (1 g) at atmospheric pressure.

When hydrogen uptake was complete (about forty-eight hours) the catalyst was removed by filtration, washed with methanol and the solvents were removed at the pump.

The oil (23 g) so obtained appeared by thin layer chromatography, to be a one to one mixture of the starting pyridine acetal and a more polar product.

The crude product was chromatographed on basic alumina (700 gm).

Elution with ether gave starting pyridine acetal (10 g).

Elution with chloroform-2% methanol gave the piperidylpyridine acetal CXXXVIII (12 g).

The piperidylpyridine acetal CXXXVIII had infrared absorption in carbon tetrachloride at 3300 cm^{-1} , 1600 and 1560 cm^{-1} , and several strong bands between 1020 and 1140 cm^{-1} .

The N.M.R. spectrum contained the following signals:

τ 8.1-8.8 (16H, multiplet), τ 7.72 (3H, singlet), τ 7.55 (1H, singlet, disappeared on D_2O exchange), τ 6.9-7.4 (7H, multiplet), τ 6.0-6.8 (4H, multiplet), τ 5.42 (1H, broad singlet), and τ 3.2 (2H, singlet).

THE PIPERIDYLPYRIDINE ALCOHOL CXXIX

The piperidylpyridine acetal CXXXVIII (12 g) was dissolved

in 5% hydrochloric acid (100 ml) and the solution was stirred at room temperature for four hours. The acidic solution was washed with two portions of ether and then basified ($\text{pH} > 10$) with ammonium hydroxide. Extraction with methylene chloride gave a brownish-yellow oil (9 g) which showed one major spot on thin layer chromatography.

Chromatography over alumina and elution with chloroform-5% methanol yielded the pure piperidylpyridine alcohol CXXXIX as a viscous yellow oil.

The product so obtained had infrared absorption in carbon tetrachloride at 3610 cm^{-1} , $3510\text{--}3100\text{ cm}^{-1}$ (broad) and 1605 , 1550 cm^{-1} (pyridine).

The N.M.R. spectrum had a three proton singlet at τ 7.7, a two proton triplet at τ 6.4 and two proton singlet at τ 3.2.

Treatment of the piperidylpyridine alcohol with acetic anhydride-pyridine converted it to an acetoxy acetamide which had infrared absorption in carbon tetrachloride at 1740 cm^{-1} and 1240 cm^{-1} (acetate), 1650 cm^{-1} (acetamide) and 1610 and 1550 cm^{-1} (pyridine).

ATTEMPTED HYDROGENATION OF THE PIPERIDYLPYRIDINE

ALCOHOL CXXXIX

The piperidylpyridine alcohol CXXXIX was not reduced when treated under the following conditions.

i) Hydrogenation at atmospheric pressure and room temperature in absolute ethanol containing acetic acid and 5% rhodium-charcoal

for eighteen hours.

ii) Hydrogenation at atmospheric pressure and room temperature in glacial acetic acid containing hydrochloric acid and platinum oxide for eighteen hours. The infrared spectrum indicated that the product so obtained was the acetate of the starting material (absorption bands at 1730 and 1240 cm^{-1} in carbon tetrachloride).

iii) Hydrogenation at fifty p.s.i. and 65°C in absolute ethanol containing acetic acid and 5% rhodium-charcoal for forty hours.

iv) Hydrogenation at 1200 p.s.i. and 60°C in absolute ethanol containing acetic acid and 5% rhodium-on-charcoal for thirty-six hours. The product obtained from this reaction was mainly starting material but a small amount of polar material also was produced indicating partial reduction may have taken place.

THE DIPIPERIDINE ALCOHOLS CXL AND CXLI

A. By catalytic hydrogenation

A solution of the piperidylpyridine alcohol CXXIX (700 mg) in absolute ethanol (10 ml) and glacial acetic acid (1 ml) containing rhodium-charcoal (400 mg) was hydrogenated at 2000 p.s.i. and 100°C for forty-two hours. The catalyst was removed by filtration and washed well with chloroform and methanol. The combined filtrates were evaporated to small volume and the residue taken up in chloroform. The chloroform solution was washed well with a 10% aqueous solution of sodium bicarbonate and the organic phase was dried over anhydrous magnesium sulfate. Evaporation of the solvent

gave an oil which showed two major spots, both of which were more polar than starting material, on thin layer chromatography.

Chromatography over alumina with chloroform-3% methanol as eluent gave the dipiperidine alcohols as a mixture of the two racemic diastereomers CXL and CXLI.

The infrared spectrum of the mixture of diastereomers contained an absorption band at 3610 cm^{-1} and strong broad absorption between 3500 and 3000 cm^{-1} in carbon tetrachloride.

The N.M.R. spectrum of the mixture contained two different methyl signals as doublets, one centered at τ 9.05 the other at τ 8.85.

The mass spectrum had a parent peak at m/e 268 with the two largest peaks in the spectrum appearing at m/e 170 and m/e 84.

B. By chemical reduction

To a refluxing solution of the piperidylpyridine alcohol CXXXIX (180 mg) in isoamyl alcohol (20 ml) was added in portions, a large excess (2 g) of sodium. After the solution was refluxed for three hours all the sodium had been consumed and the original yellow solution had become colorless. Water (5 ml) was added carefully to the cooled reaction mixture and the contents of the reaction flask were poured into cold dilute hydrochloric acid. The acidic solution was washed thoroughly with ether to remove isoamyl alcohol. Basification of the aqueous phase with cold aqueous ammonium hydroxide followed by extraction with methylene chloride gave a nearly colorless oil (100 mg)

which proved to be identical (thin layer chromatographic behavior, infrared spectrum in carbon tetrachloride) with the mixture of dipiperidine alcohols obtained by catalytic hydrogenation of the piperidylpyridine alcohol CXXXIX (see above).

ACETYLATION OF THE DIPIPERIDINE ALCOHOLS CXL AND CXLI

The mixture of dipiperidine alcohols CXL and CXLI (35 mg) was dissolved in a mixture of acetic anhydride (1 ml) and pyridine (2 ml) and allowed to stand at room temperature for eighteen hours. The solvents were removed under reduced pressure and the residues were taken up in chloroform. The chloroform solution was washed first with a portion of 10% aqueous potassium carbonate and then with a portion of dilute hydrochloric acid. The residual chloroform layer was dried over anhydrous magnesium sulfate and the solvent was removed at the pump leaving the O-acetyldiacetamides as a pale brown oil (45 mg) which showed two spots with nearly the same R_f on thin layer chromatography.

The mixture of O-acetyldiacetamides showed infrared absorption at 1735 and 1240 cm^{-1} (OAc) and 1635 cm^{-1} (acetamide) in carbon tetrachloride. The band at 1635 cm^{-1} was more intense than that at 1735 cm^{-1} .

THE TRICYCLIC N-H COMPOUNDS CXLII AND CXLV

A solution of the mixture of dipiperidine alcohols CXL and CXLI (70 mg) in 48% hydrobromic acid (10 ml) was refluxed for sixteen

hours. The cooled reaction mixture was poured into water (20 ml) and was neutralized by careful addition of small portions of solid sodium carbonate. After each addition of sodium carbonate the aqueous solution was shaken with chloroform. The chloroform extracts were combined and refluxed over anhydrous sodium carbonate for four hours, filtered and the solvent removed at the pump yielding a brown oil (60 mg) which showed two major spots with nearly the same R_f value both running faster than the starting materials on thin layer chromatography.

Chromatography over alumina (2 g) with chloroform as eluent gave the mixture of the two tricyclic N-H compounds CXLII and CXLV.

The mixture of tricyclic compounds had infrared absorption bands in carbon tetrachloride at 3280 cm^{-1} and at 2800, 2740 and 2620 (shoulder) cm^{-1} .

The mass spectrum of the mixture of tricyclic compounds had a parent peak at m/e 250. and a base peak at m/e 152 and was virtually identical with that of the tricyclic N-H compound CXLII obtained by S. Valverde-Lopez from the natural series. Calculated for $\text{C}_{16}\text{H}_{30}\text{N}_2$: molecular wt. 250.2409. Found: 250.2411.

THE TRICYCLIC N-METHYL COMPOUNDS CXLVI AND CXLVII

A solution of the mixture of tricyclic N-H compounds CXLII and CXLV (20 mg) in formic acid (1 ml) and formaldehyde (1 ml) was gently refluxed for eighteen hours. The cooled reaction mixture was then poured into an aqueous 5% sodium hydroxide solution and the

product was extracted thoroughly with ether. Evaporation of the solvent gave an oil (20 mg) which showed two spots running very close together on thin layer chromatography.

The infrared spectrum of the mixture of tricyclic N-methyl compounds in carbon tetrachloride no longer showed N-H absorption and had "Bohlmann bands" at 2780, 2710, and 2610 cm^{-1} .

The mass spectrum of the mixture of tricyclic N-methyl compounds CXLVI and CXLVII had a parent peak at m/e 264, and had only two other significant peaks at m/e 152 (44%) and m/e 98 (100%). The mass spectrum of the synthetic mixture was nearly identical with that of the tricyclic N-methyl compound prepared by S. Valverde-Lopez from the natural series.

SEPARATION OF THE TRICYCLIC N-H COMPOUNDS CXLII AND CXLV

A crude mixture of the two tricyclic N-H compounds (250 mg) was subjected to careful column chromatography on alumina (12 g). The following table describes the fractions taken and the amount of product obtained. The fractions were monitored by thin layer chromatography. Fractions 1-3 contained only faster running impurities. Fraction 4 contained both tricyclic N-H compounds but appeared to be enriched in the faster running of the two components. The remaining fractions were composed of mixtures of the two tricyclic N-H compounds although fraction 7 and 8 were enriched in the slower running component.

Fraction No.	Eluent	Vol. (ml)	Wt. of Product
1	CH ₂ Cl ₂	100	14 mg
2	CH ₂ Cl ₂ /CHCl ₃	80/20	30 mg
3	"	70/30	60 mg
4	"	60/40	32 mg
5	"	50/50	23 mg
6	"	40/60	23 mg
7	"	30/70	17 mg
8	"	20/80	14 mg
9	"	10/90	5 mg

Fraction 4 was subjected to gas-liquid chromatography on an Aerograph Manual Temperature Programmer Gas Chromatograph using a commercially prepared 5 ft. x 1/4 in. 10% QF1 on Chromosorb W column. Column temperature: 148°C, Helium Flow Rate : 60 cc/min.

The major fraction which, had a retention time of six and one half minutes, was collected. The infrared spectrum in carbon tetrachloride of the tricyclic N-H compound CXLII so obtained was identical with that of the tricyclic N-H compound prepared from the natural series by S. Valverde-Lopez. The tricyclic N-H compound obtained from the natural series had the same retention time on gas chromatography as the synthetic tricyclic N-H compound.

Fraction 7 was subjected to gas-liquid chromatography on a

Q-F1 column under the conditions described above. The major component, which had a retention time of five minutes and ten seconds, was collected.

The infrared spectrum in carbon tetrachloride of the tricyclic N-H compound CXLV so obtained showed N-H absorption at 3290 cm^{-1} and was different from that of the tricyclic N-H compound obtained from the natural series.

THE TETRACYCLIC COMPOUNDS CL, CLIV AND CLV

A. By sulfoxide-carbodiimide oxidation of the dipiperidine alcohols CXL and CXLI.

To a solution of a mixture of the dipiperidine alcohols CXL and CXLI (134 mg, 0.5 mmole), obtained from catalytic hydrogenation of the piperidylpyridine alcohol CXXXIX, in dry dimethylsulfoxide (2 ml), pyridine (39.5 mg, 0.5 mmole) and trifluoroacetic acid (143 mg, 1.25 mmole), was added dicyclohexylcarbodiimide (270 mg, 1.5 mmole). Soon after the reaction was begun colorless crystals began to separate. The reaction mixture was allowed to stand at room temperature for eighteen hours after which time the crystalline material was separated by filtration and washed well with methylene chloride. The combined filtrates were extracted thoroughly with three portions of dilute hydrochloric acid. The combined acidic extracts were basified with cold aqueous ammonium hydroxide and extracted with four portions of methylene chloride. The combined organic extracts were back-washed with five (50 ml) portions of water and were then dried over anhydrous

magnesium sulfate. Evaporation of the solvent gave a brown semi-solid which showed only two spots on thin layer chromatography both running much faster than the dipiperidine alcohols CXL and CXLI.

The crude product was chromatographed on alumina (6 g).

Elution with methylene chloride-chloroform (9:1) gave the faster running tetracyclic material CL as a colorless solid (25 mg), m.p. of a sublimed sample 62-64°C.

The tetracyclic material so obtained was identical (thin layer chromatography, infrared spectrum in carbon tetrachloride, mass spectrum) with dihydrodeoxyepiallocernuine obtained by S. Valverde-Lopez from the natural series.

The N.M.R. spectrum of the synthetic material contained a three proton doublet at τ 9.15 ($J=6$ cps), a one proton multiplet at τ 7.65 ($W_{1/2}=15$ cps) and a one proton broadened doublet at τ 6.83 ($J=9$ cps).

Calculated for $C_{16}H_{28}N_2$: molecular weight 248.2253.

Found: 248.2249.

A sample of CL was sublimed for analysis. Anal: Calcd. for $C_{16}H_{28}N_2$: C, 77.36; H, 11.38; N, 11.28. Found: C, 77.33, 77.11; H, 11.12, 10.90; N, 11.57.

Elution with methylene chloride-chloroform (7:3) gave the slower running tetracyclic materials CLIV and CLV as an oil (20 mg) which showed only one spot on thin layer chromatography.

The infrared spectrum in carbon tetrachloride of the oil was different from that of the synthetic "dihydrodeoxyepiallocernuine" CL, although the mass spectrum was virtually identical with the mass spectrum of the faster running tetracyclic material.

The N.M.R. spectrum of the oil had a doublet at τ 9.16 ($J \approx 5.5$ cps) and another doublet at τ 9.07 ($J \approx 6$ cps) indicating the presence of two components in the oil.

Calculated for $C_{16}H_{28}N_2$: molecular weight 248.2253.

Found: 248.2251.

The same mixture of tetracyclic components was obtained by sulfoxide-carbodiimide oxidation of the mixture of dipiperidine alcohols CXL and CXLI obtained from chemical reduction of the piperidylpyridine alcohol CXXXIX.

B. By chromium trioxide-pyridine oxidation of the dipiperidine alcohols CXL and CXLI

A solution of the mixture of dipiperidine alcohols CXL and CXLI (45 mg) in pyridine (4 ml) was added to a slurry of chromium trioxide (70 mg) in pyridine (1 ml) at 0°C . Stirring was continued at 0°C for eight hours and then the reaction mixture was allowed to warm to room temperature and stirring continued for an additional eight hours. The reaction mixture was poured into cold aqueous ammonium hydroxide and the product was extracted with four portions of chloroform. The chloroform solution was evaporated to dryness under reduced pressure

and the residues were taken up in fresh chloroform and washed with five portions of water. The chloroform layer was separated, dried over anhydrous magnesium sulfate and evaporated leaving a brown semi-solid (30 mg). This semi-solid was composed of the same mixture of tetracyclic materials as was obtained by sulfoxide-carbo-diimide oxidation of the dipiperidine alcohols CXL and CXLI.

The same mixture of tetracyclic materials was obtained in somewhat lower yield by oxidation of the dipiperidine alcohols CXL and CXLI with:

- i) Chromium trioxide in 95% acetic acid at room temperature for twenty-four hours.
- ii) Jones' reagent (chromium trioxide in sulfuric acid and acetone) at room temperature for five minutes.

SEPARATION OF THE DIPIPERIDINE ALCOHOLS CXL AND CXLI

A. Formylation of the dipiperidine alcohols CXL and CXLI

The mixture of dipiperidine alcohols CXL and CXLI (280 mg) was dissolved in dimethoxyethane (5 ml), acetic-formic anhydride (1 ml) was added and the reaction mixture was stirred at room temperature for sixteen hours. After removal of the solvents under reduced pressure, the residues were taken up in water and poured into aqueous ammonium hydroxide. Chloroform extraction gave a brown oil which was dissolved in methanol-water 1:1 (40 ml). Sodium carbonate (2 gm) was added and the resulting mixture was stirred at room temperature for two hours.

The reaction mixture was then poured into water (50 ml) and extracted with chloroform. The combined chloroform extracts were washed with two portions of dilute hydrochloric acid to remove basic materials and the residual chloroform layer was dried over anhydrous magnesium sulfate and evaporated to dryness giving a pale yellow oil (220 mg) which showed two slightly separated spots on thin layer chromatography.

B. Chromatography of the diformamides CLVII and CLVIII

The mixture of diformamides CLVII and CLVIII (220 mg) obtained above was chromatographed on a column of alumina (50 g) using an automatic fraction collector which was set to collect 5 ml fractions. Thin layer chromatography was used to monitor the fractions. The results of the chromatography are shown below.

Fraction No.	Eluent	Amount Eluted
1-220	$\text{CHCl}_3:\text{CH}_2\text{Cl}_2$ (9:1)	nil
220-630	CHCl_3	100 mg
630-690	$\text{CHCl}_3:1/2\%$ MeOH	40 mg
690-820	$\text{CHCl}_3:1/2\%$ MeOH	60 mg

Fractions 220-630 contained only the faster running of the two diformamides CLVII. We have designated this compound as N-formyl A.

The infrared spectrum of N-formyl A (CLVII) in carbon

tetrachloride had hydroxyl absorption at 3620 and 3450 cm^{-1} and a strong band at 1670 cm^{-1} due to the N-formyl groups.

The fractions 630-690 contained a mixture of the diformamides.

The fractions 690-820 contained only the slower running of the two diformamides (CLVIII) which has been designated N-formyl B.

The infrared spectrum of N-formyl B (CLVIII) in carbon tetrachloride had hydroxyl absorption at 3610 and 3400 cm^{-1} and N-formyl absorption at 1675 cm^{-1} .

C. Hydrolysis of the diformamides

i) Hydrolysis of N-formyl A (CLVII)

A solution of N-formyl A (CLVII) (40 mg) in 5% aqueous sulfuric acid was refluxed for fourteen hours. The cooled reaction mixture was poured into ice cold aqueous ammonium hydroxide. Chloroform extraction gave the dipiperidine alcohol CXL as a colorless oil (25 mg) which showed only one spot on thin layer chromatography having the same R_f as the faster running of the two dipiperidine alcohols CXL and CXLI.

ii) Hydrolysis of N-formyl B (CLVIII)

The hydrolysis of N-formyl B (CLVIII) was carried out in the same way as that of N-formyl A. The dipiperidine alcohol CXLI so obtained was a colorless semi-solid which had the same R_f on thin layer chromatography as the slower running of the two dipiperidine alcohols.

The molecular weight of the dipiperidine alcohol CXLI was found to be 268.2510. Calculated for $\text{C}_{16}\text{H}_{32}\text{N}_2\text{O}$: 268.2514.

A sample was sublimed for analysis.

Anal. Calcd. for $C_{16}H_{32}N_2O$: C, 71.59; H, 12.02; N, 10.44.

Found: C, 71.30, 71.43; H, 11.61, 11.72; N, 9.85.

OXIDATION OF THE DIPIPERIDINE ALCOHOL CXL

A solution of the dipiperidine alcohol CXL (15 mg) in pyridine (4 ml) was added to a slurry of chromium trioxide (25 mg) in pyridine (0.5 ml) at 0°C. The reaction mixture was stirred at 0°C for eight hours then at room temperature for an additional eight hours. The reaction mixture was poured into ice cold aqueous ammonium hydroxide and the product was extracted thoroughly with chloroform. The chloroform extracts were backwashed with water, dried over anhydrous magnesium sulfate and evaporated to dryness. The product so obtained was identical (thin layer chromatographic behavior, infrared spectrum) with the dihydrodeoxyepiallocernuine (CL) previously obtained.

OXIDATION OF THE DIPIPERIDINE ALCOHOL CXLI

The procedure used for the oxidation of the dipiperidine alcohol CXL (above) was also used for the oxidation of the dipiperidine alcohol CXLI. The product so obtained was identical (thin layer chromatographic behavior, infrared spectrum in carbon tetrachloride) with the mixture of tetracyclic products CLIV and CLV previously obtained.

INFRARED SPECTRA

Figure 13

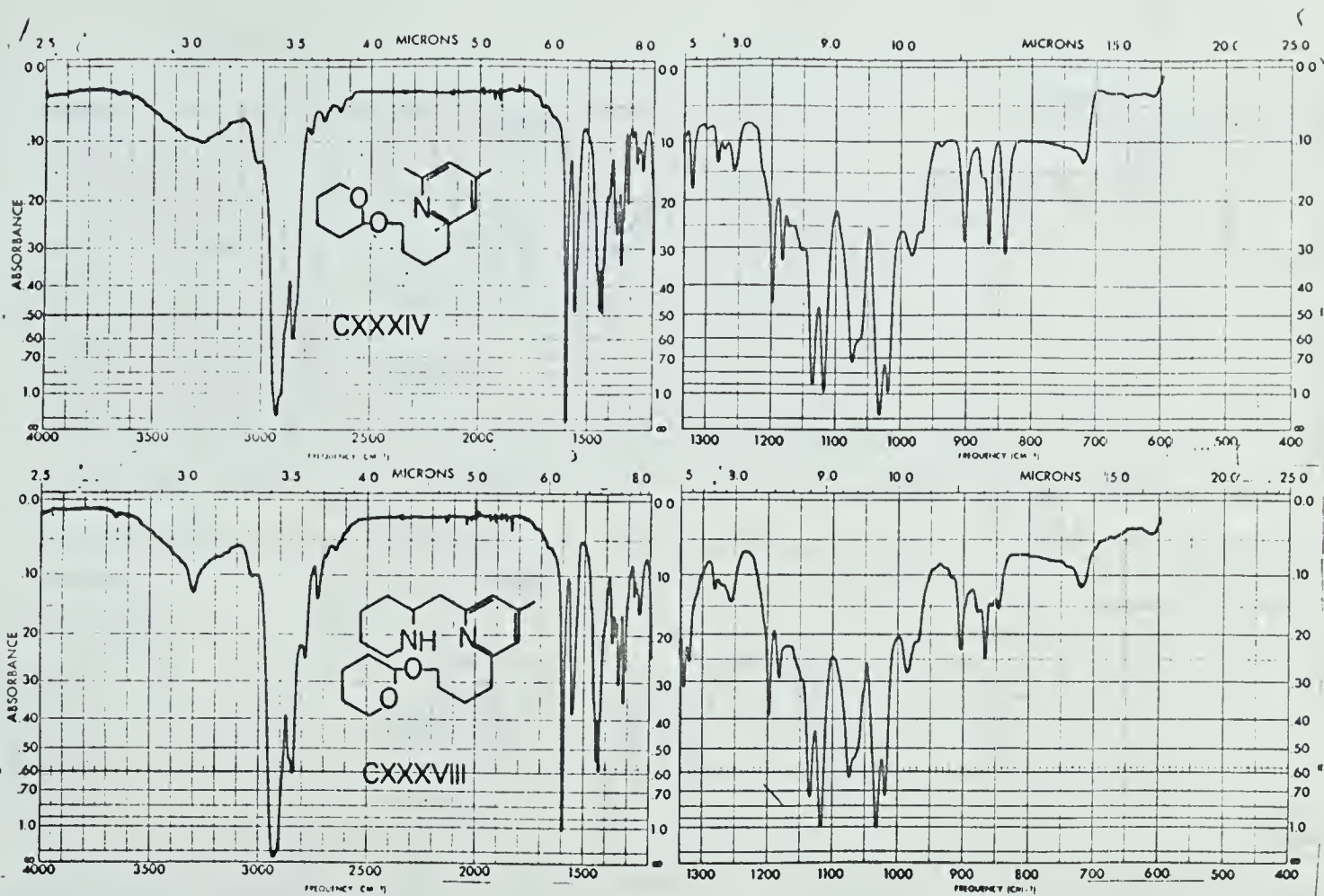


Figure 14

Figure 15

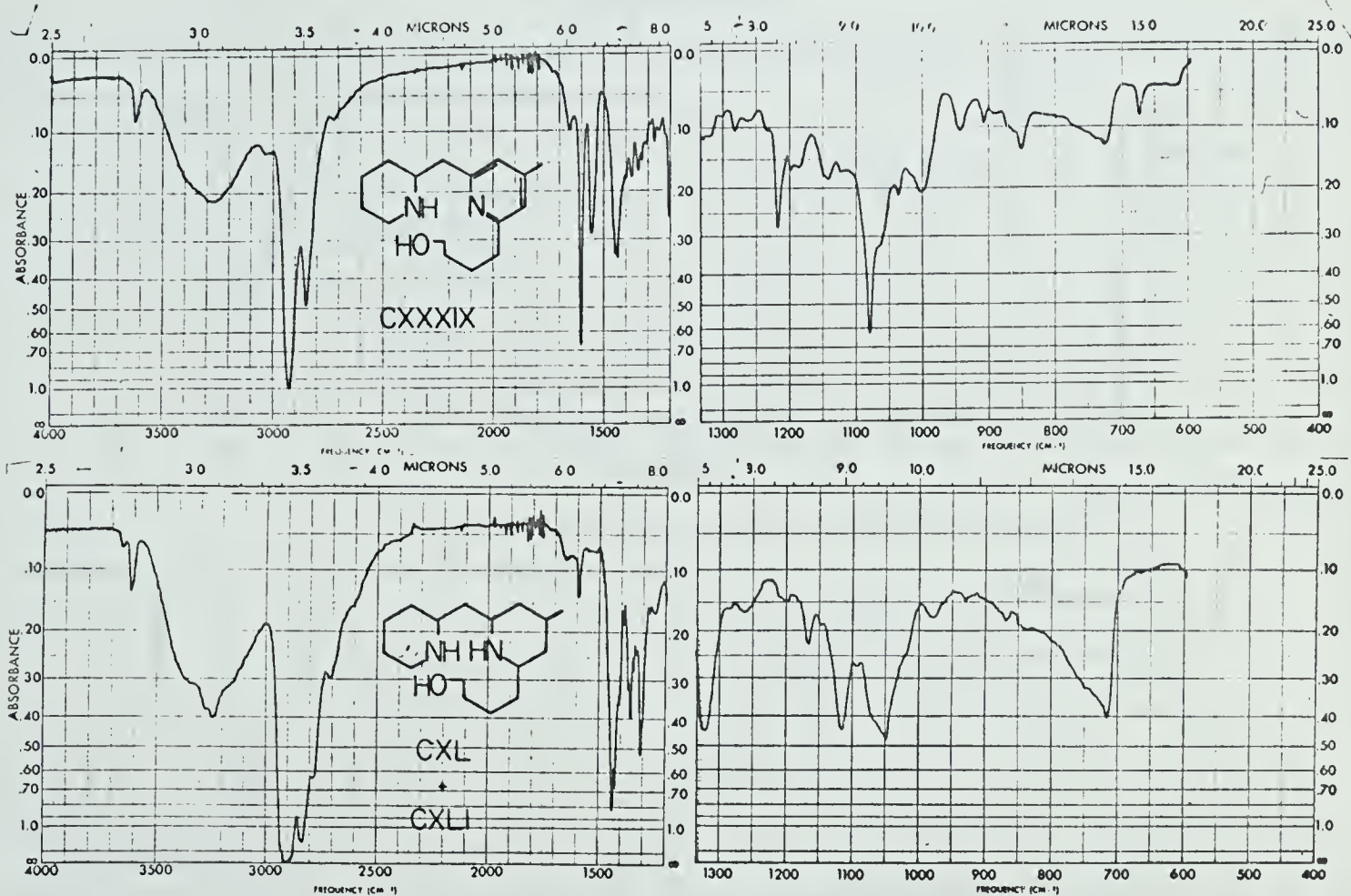


Figure 16

Figure 17

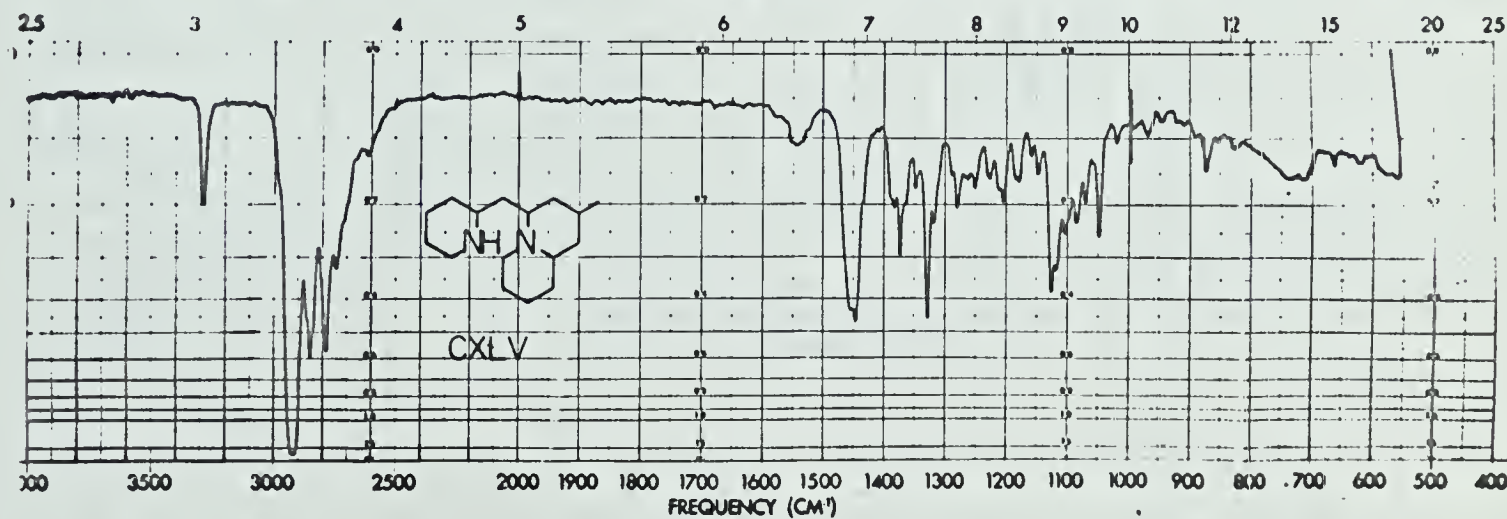
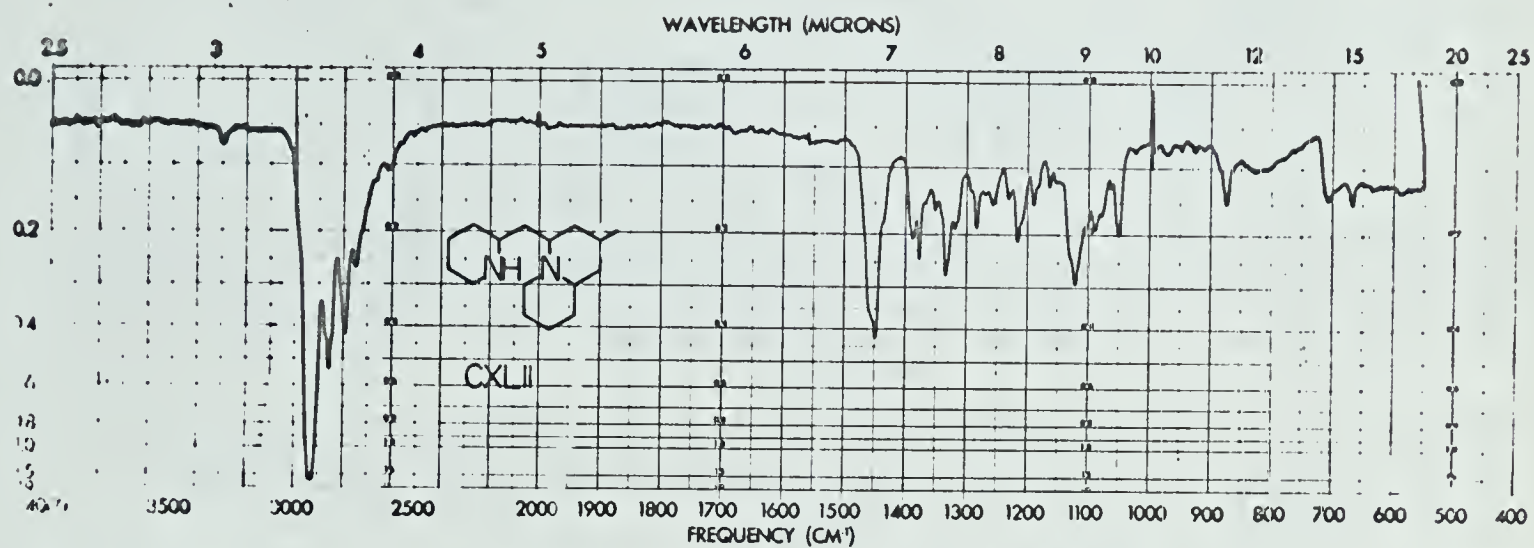


Figure 18

Figure 20

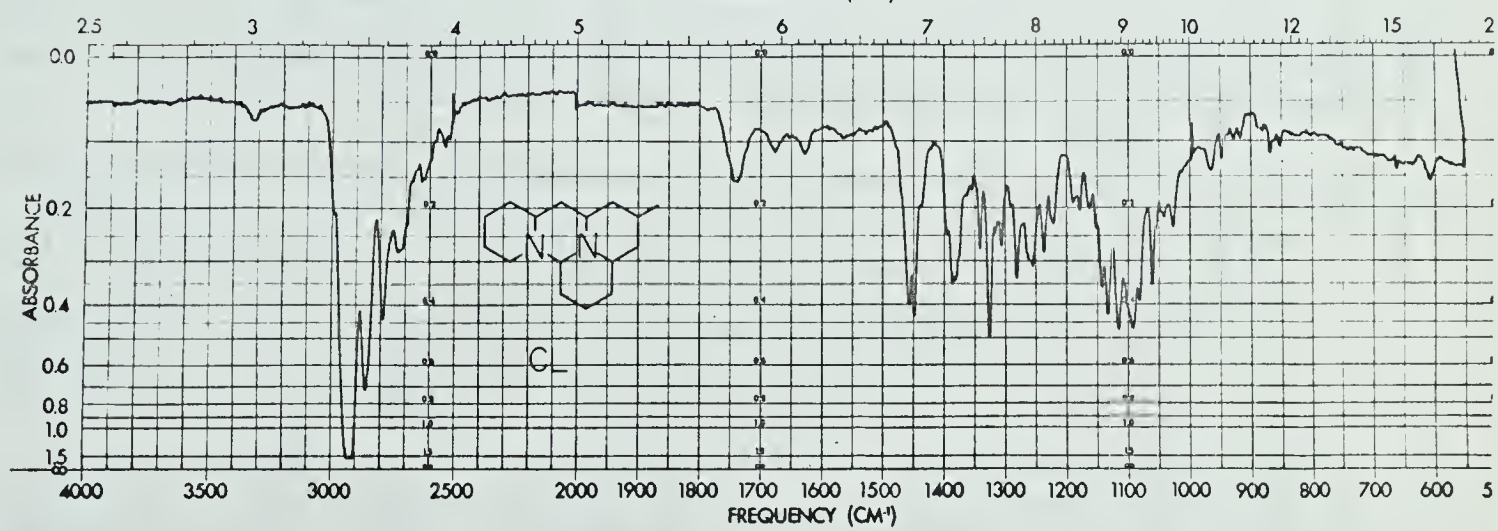
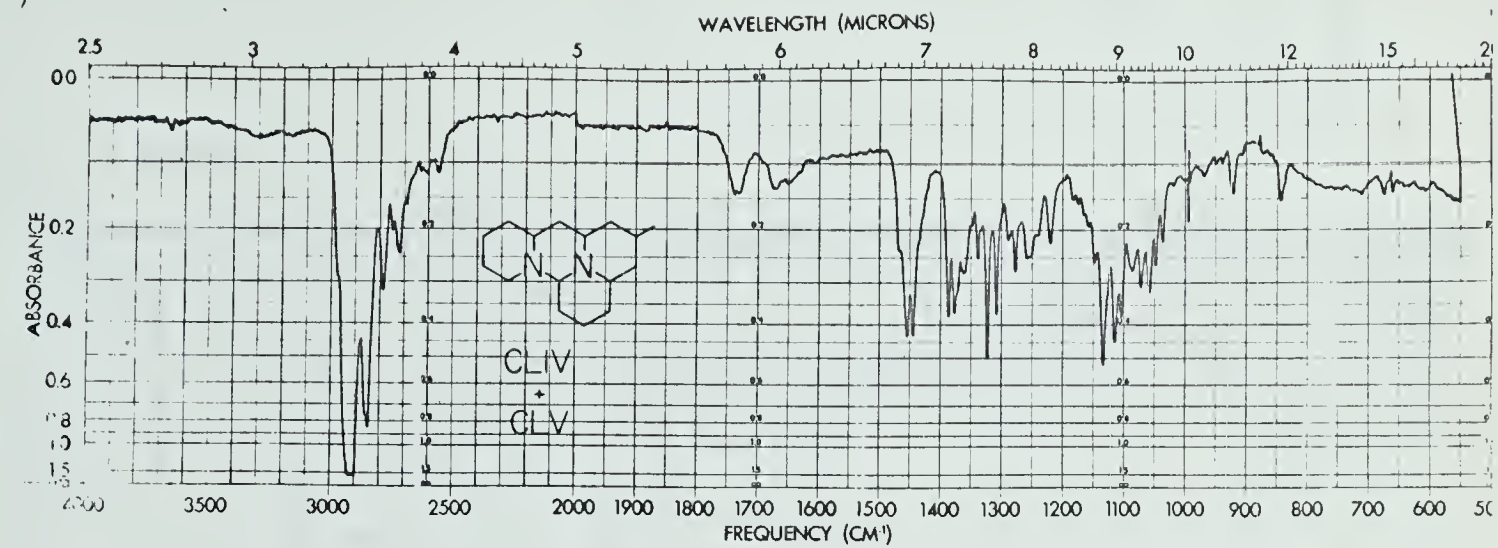


Figure 19

Figure 21

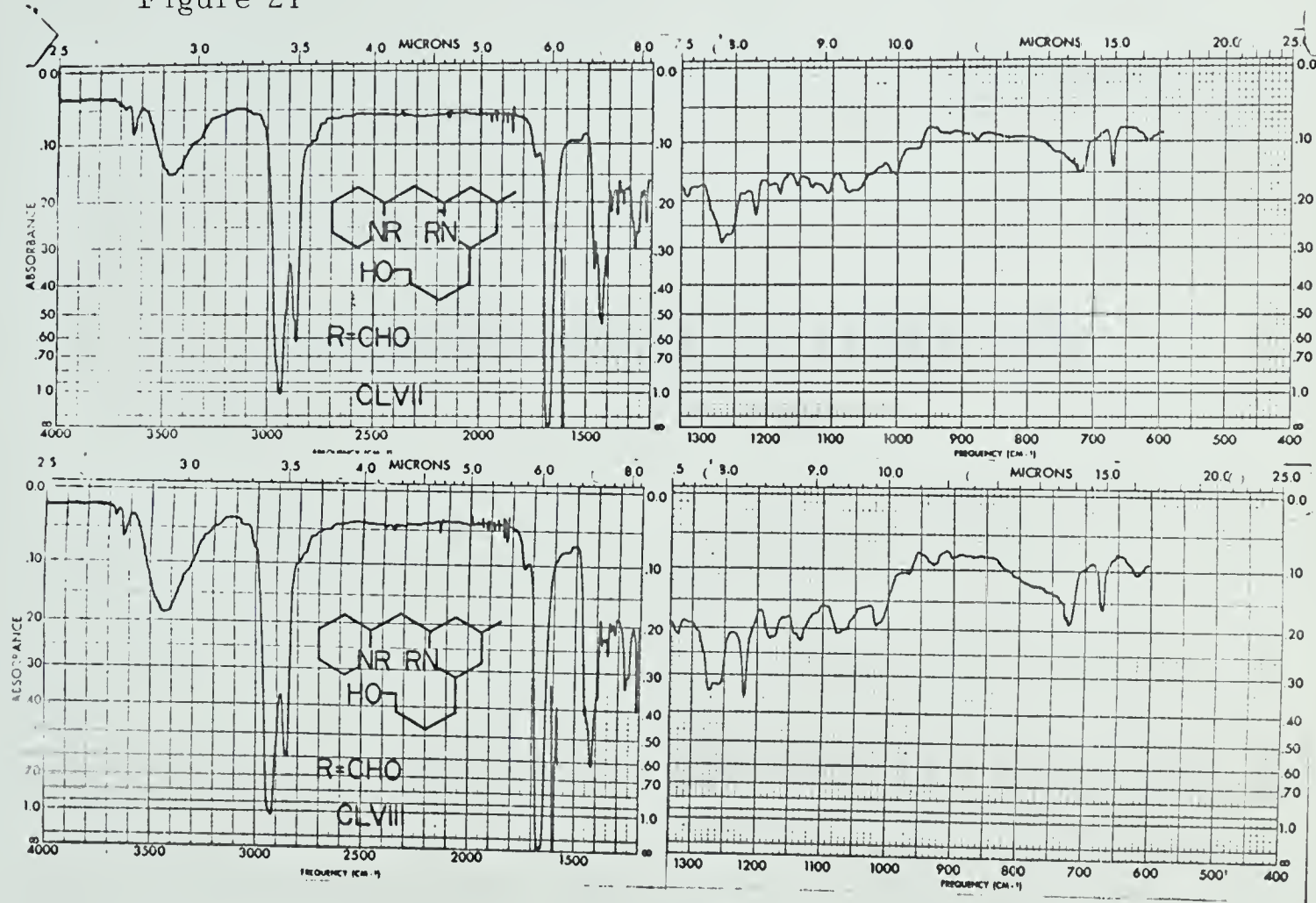


Figure 22

NUCLEAR MAGNETIC RESONANCE
SPECTRA

Figure 23

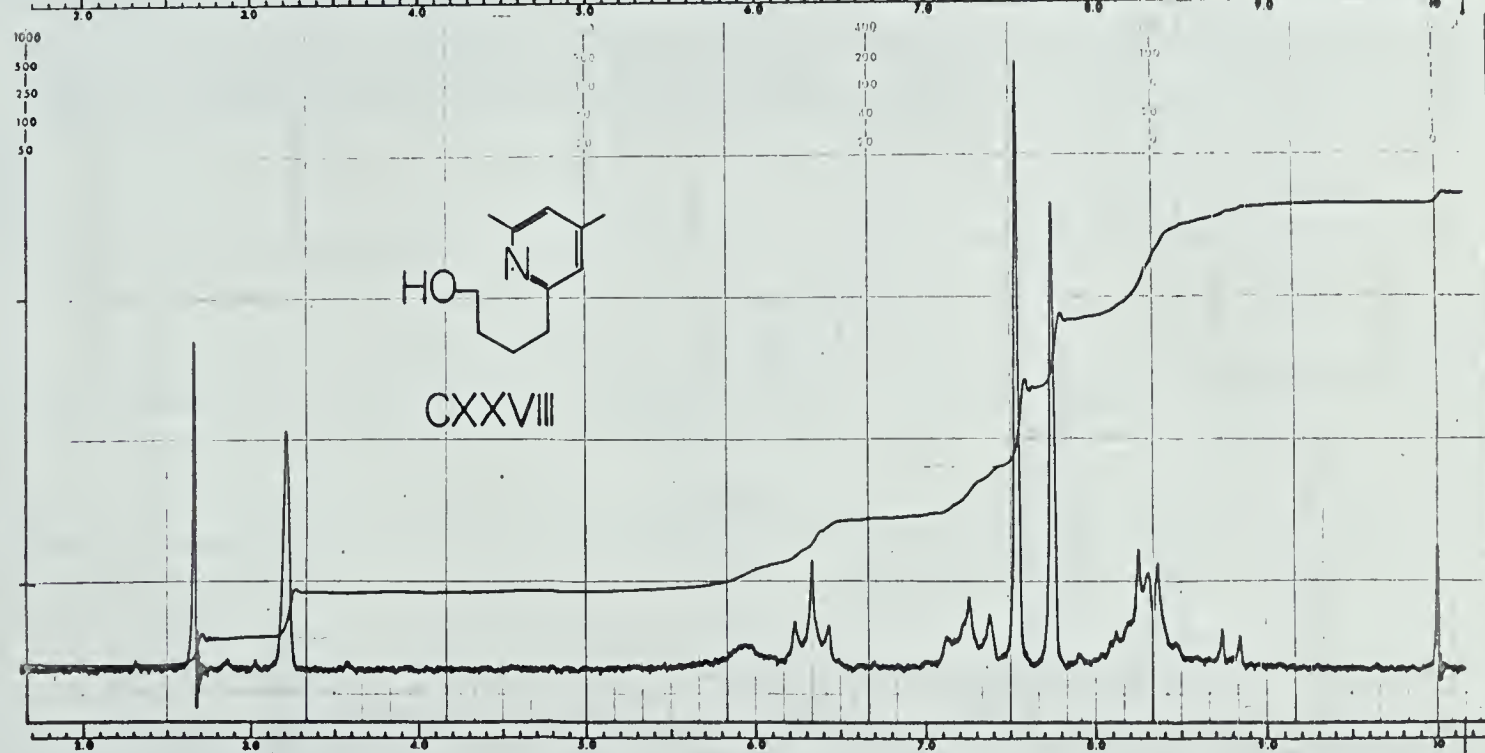
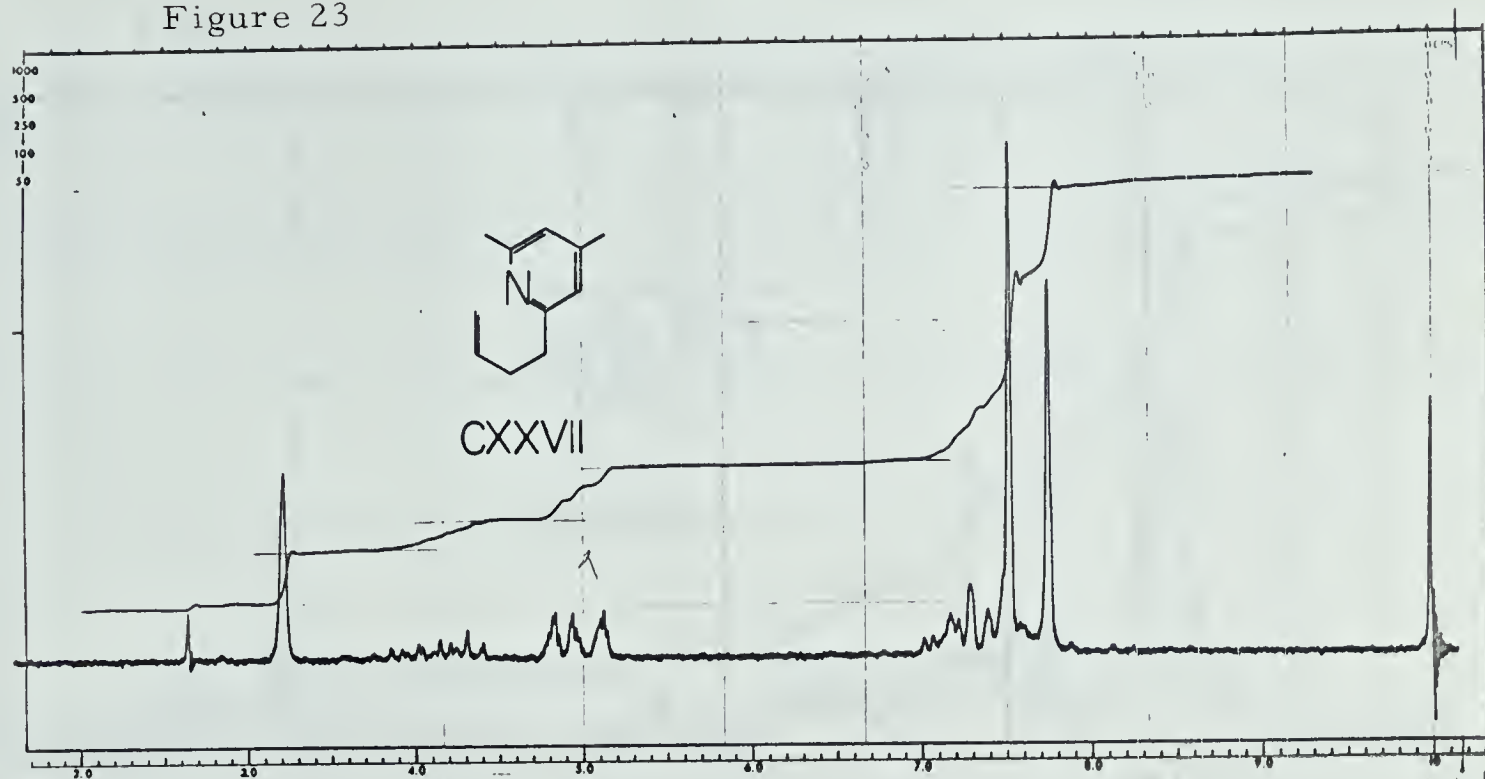


Figure 24

Figure 26

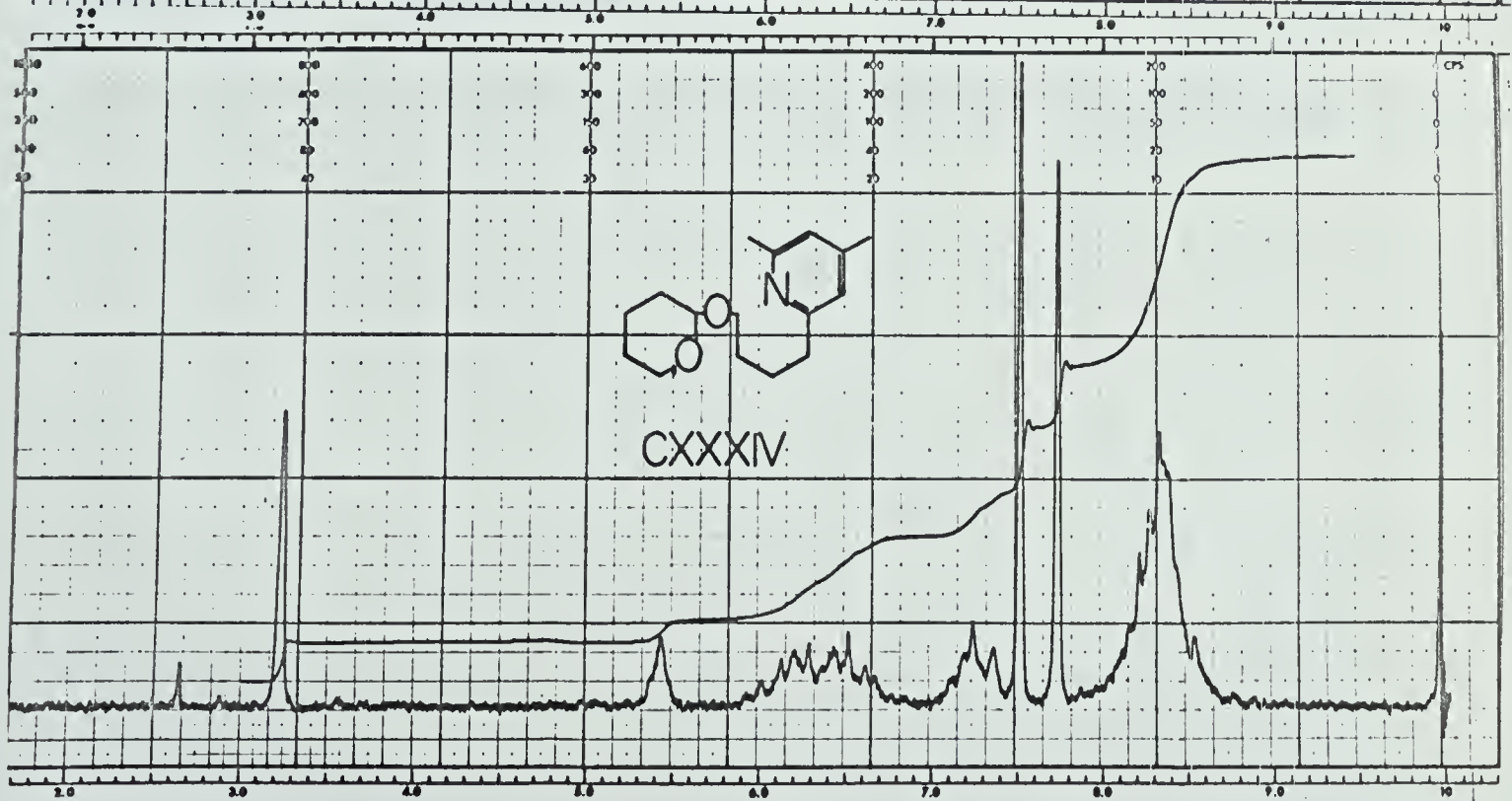
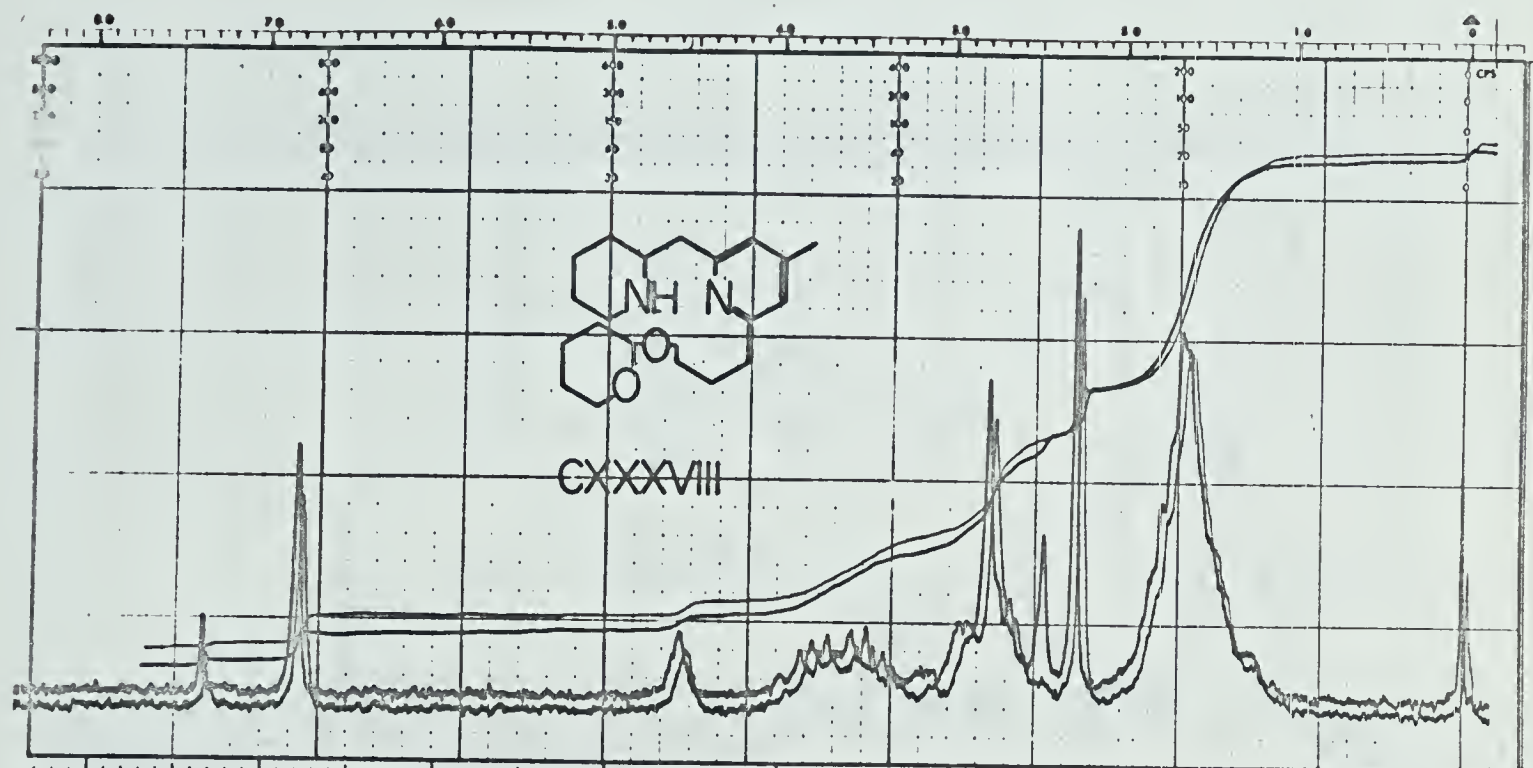


Figure 25

Figure 27

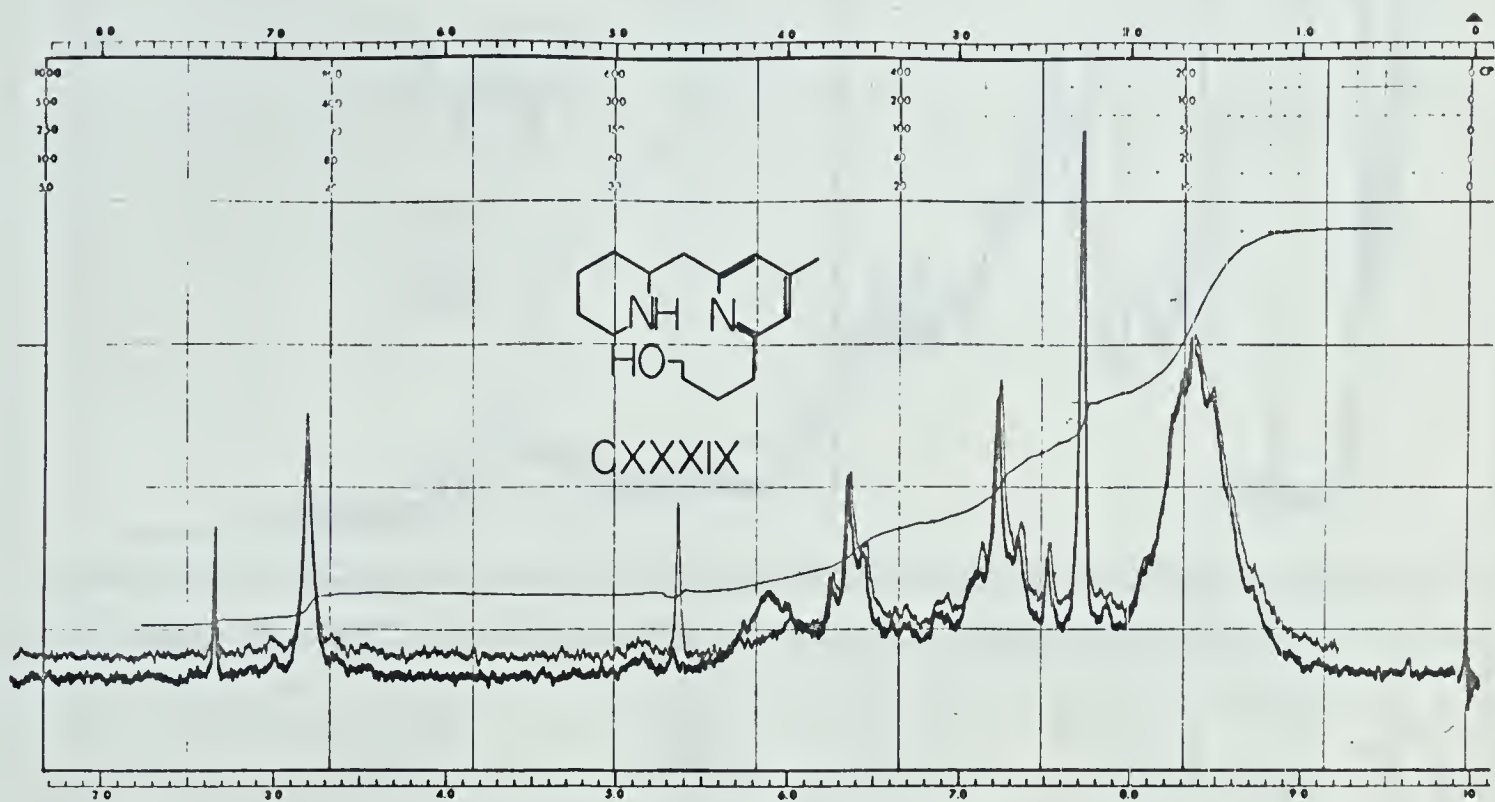


Figure 29

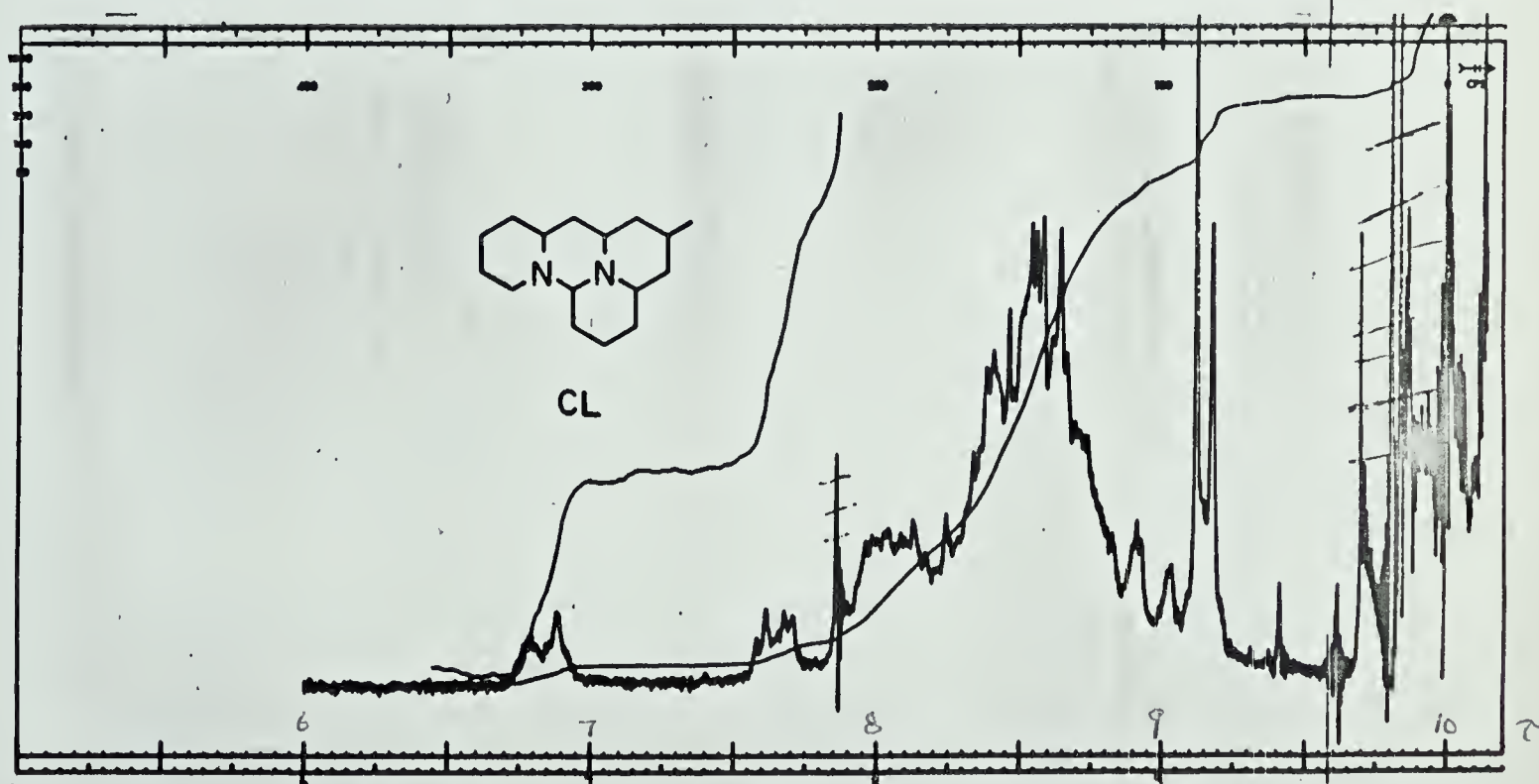
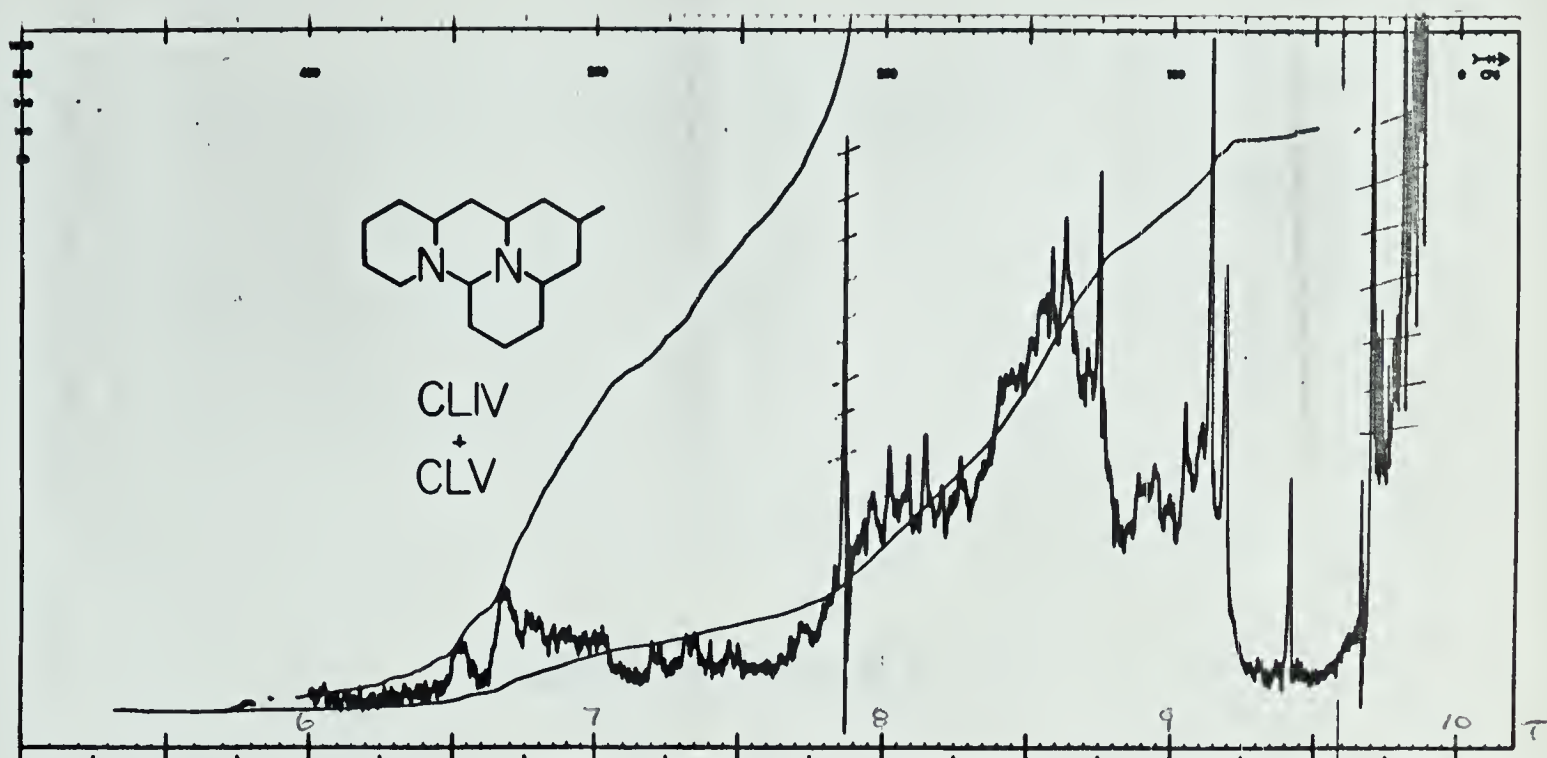


Figure 28

MASS SPECTRA

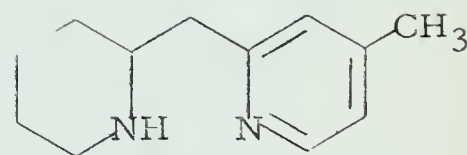
TABLE 6

2-(2-Piperidylmethyl)-4-methylpyridine CVIII

M.W.: 190

Temperature: 200°C

Electron Energy: 70 e.v.



CVIII

m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
190	0.8	106	9	65	13
189	3.8	97	16	56	11
108	13.1	85	6	55	12
107	76	84	100		

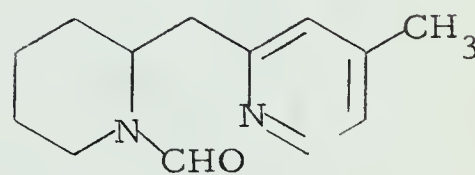
TABLE 7

N-Formylpiperidylpyridine CXI

M.W.: 218

Temperature: 200°C

Electron energy: 70 e.v.



CXI

m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
218	5	108	20	65	8
190	7	107	100	56	26
189	44	106	10	55	11
113	7	97	7		
112	96	84	76		

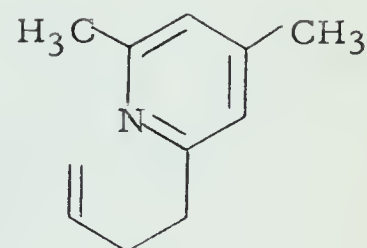
TABLE 8

2-(3-Butenyl)-4,6-dimethylpyridine CXXVII

M.W.: 161

Temperature: 200°C

Electron Energy: 70 e.v.



CXXVII

m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
161	8	144	33	119	20
160	63	143	8	106	25
159	100	133	40	78	20
145	46	120	56	76	27

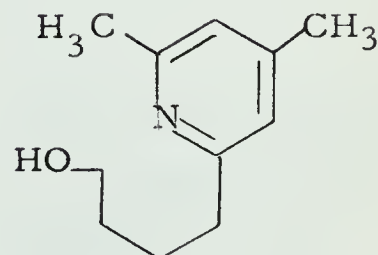
TABLE 9

The pyridine alcohol CXXVIII

M.W.: 179

Temperature: 200°C

Electron Energy: 70 e.v.



CXXVIII

m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
179	3	145	10	106	22
178	6	135	30	93	10
162	21	134	100	91	12
161	10	133	8	79	28
160	15	121	35	77	35
148	91	120	25		
146	74	107	24		

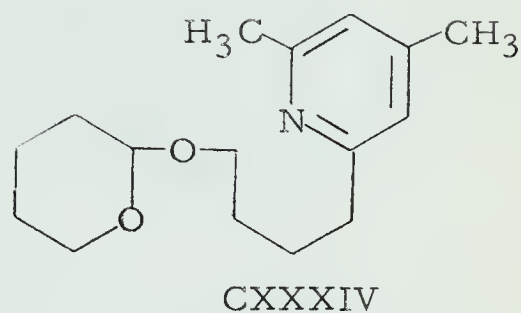
TABLE 10

The pyridine acetal CXXXIV

M.W.: 263

Temperature: 185°C

Electron Energy: 70 e.v.



m/e	% B.P.	m/e	% B.P.
263	0.2	148	19
179	5	134	21
178	32	121	100
163	12	120	4
162	74	85	19

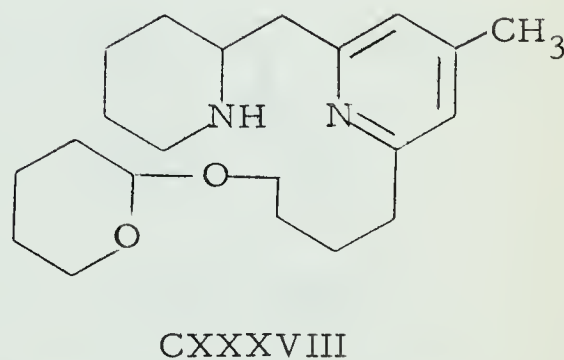
TABLE 11

The piperidylpyridine acetal CXXXVIII

M.W.: 346

Temperature: 200°C

Electron Energy: 70 e.v.



m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
263	2	160	10	84	54
261	4	148	26	77	14
180	9	134	36	56	16
179	33	122	12	55	60
178	14	121	100	54	16
163	9	120	12		
162	40	85	24		

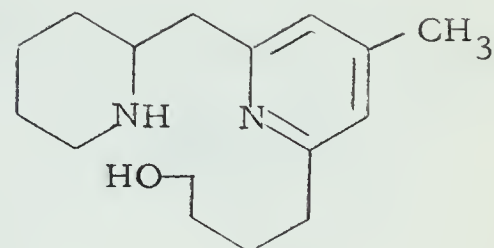
TABLE 12

The piperidylpyridine alcohol CXXXIX

M.W.: 262

Temperature: 200°C

Electron Energy: 70 e.v.



CXXXIX

m/e	% B.P.	m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
262	0.2	160	8	134	40	106	8
261	0.7	148	33	122	10	84	4
179	10	146	7	121	100	83	13
162	5	135	10	120	16	55	30
161	4			107	8		

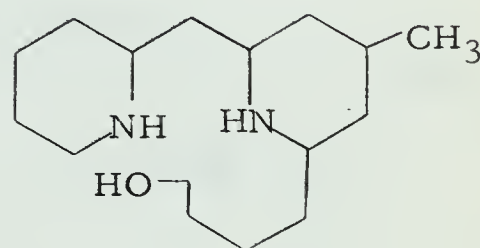
TABLE 13

The dipiperidine alcohols CXL and CXLI

M.W.: 268

Temperature: 200°C

Electron Energy: 70 e.v.



CXL + CXLI

m/e	% B.P.	m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
268	23	184	16	111	17	84	100
219	14	183	20	110	39	83	10
210	16	170	68	98	47	82	14
207	12	152	21	97	42	70	17
196	36	124	32	96	15	69	14
195	36	112	27	85	7	55	26

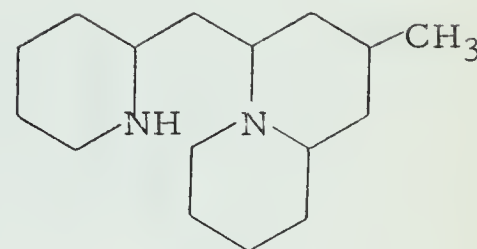
TABLE 14

The tricyclic N-H compounds CXLII and CXLV

M.W.: 250

Temperature: 185°C

Electron Energy: 70 e.v.



CXLII + CXLV

m/e	% B.P.	m/e	% B.P.
250	12	124	18
167	12	110	18
166	18	97	15
153	16	84	44
152	100		

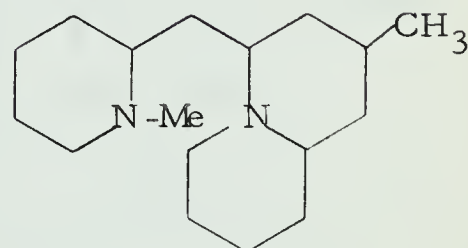
TABLE 15

The tricyclic N-methyl compounds CXLVI and CXLVII

M.W.: 264

Temperature: 185°C

Electron Energy: 70 e.v.



CXLVI and CXLVII

m/e	% B.P.	m/e	% B.P.
264	14	152	43
205	9	98	100
178	9		
166	8		
165	13		

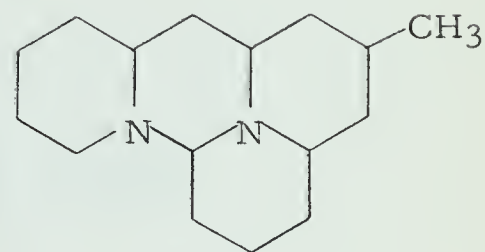
TABLE 16

Synthetic dihydrodeoxyepialloceraine CL

M.W.: 248

Temperature: 185°C

Electron Energy: 70 e.v.



CL

m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
248	33	206	24	84	9
247	38	205	32	55	10
220	22	164	7		
219	100	150	9		

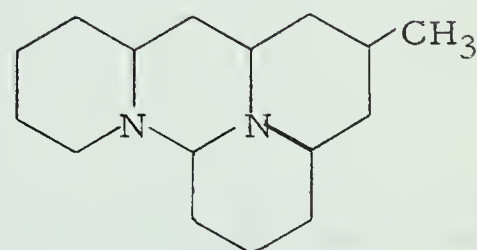
TABLE 17

The tetracyclic compounds CLIV and CLV

M.W.: 248

Temperature: 185°C

Electron Energy: 70 e.v.

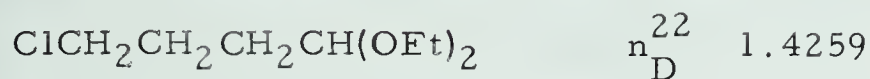


CLV and CLIV

m/e	% B.P.	m/e	% B.P.	m/e	% B.P.
248	39	206	27	84	11
247	33	205	31	55	11
220	26	164	11		
219	100	150	9		

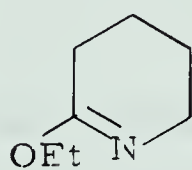
ADDENDUM

The Chloroacetal CXV



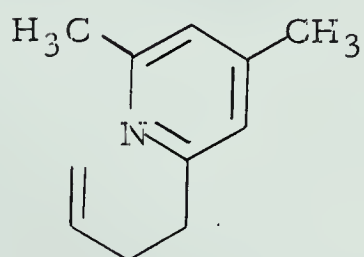
CXV

Iminoester of Velerolactam CVI


 $n_{\text{D}}^{21} \quad 1.4554$
Mass Spectrum: m/e 127; 99; 83

CVI

2-(3-Butenyl)-4,6-dimethylpyridine CXXVII


 $n_{\text{D}}^{21} \quad 1.5042$
Mass spectrum: Calc. for $\text{C}_{11}\text{H}_{15}\text{N}$: 161.1204

Measured: 161.1907

Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{N}$: C, 81.92; H, 9.38; N, 8.69.

Found: C, 81.22, 81.11; H, 8.94, 9.13; N, 8.84.

CXXVII

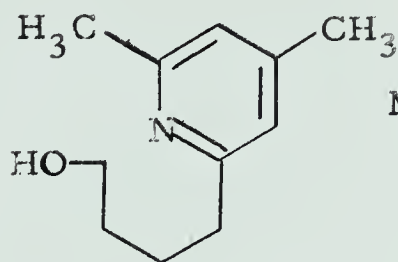
Chloroplatinate:

Anal. Calcd. for $\text{C}_{22}\text{H}_{30}\text{N}_2 \cdot \text{H}_2\text{PtCl}_6$: C, 36.07;

H, 4.40; N, 3.82.

Found: C, 35.71, 35.76; H, 4.72, 4.70; N, 3.49.

The Pyridine Alcohol CXXVIII



CXXVIII

Mass Spectrum: Calc. for $C_{11}H_{17}NO$: 179.1310

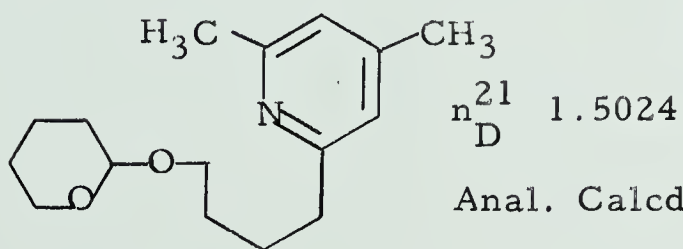
Found: 179.1307

p-nitrobenzoate

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14.

Found: C, 65.57, 65.36; H, 5.97, 6.02.

The Pyridine Acetal CXXIV



CXXIV

n_D^{21} 1.5024

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57, N, 5.32.

Found: C, 72.72, 72.91; H, 9.48, 9.51; N, 5.32.

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